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의학박사 학위논문

한국판 Mini-Mental State
Examination-2 의 타당화 및
임상적 유용성 연구

The study about the validity and
clinical usefulness of the Korean
version of the Mini-Mental State
Examination-2

2018 년 2 월

서울대학교 대학원

의학과 중개의학 전공

백 민 재

한국판 Mini-Mental State Examination-2의 타당화 및 임상적 유용성 연구

The study about the validity and clinical usefulness of the Korean version of the Mini-Mental State Examination-2

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이 논문을 의학박사 학위논문으로 제출함.

2017 년 10 월
서울대학교 대학원
의학과 중개의학 전공
백 민 재

백민재의 의학박사 학위논문을 인준함.

2018 월 1 월

위원장 _____ (인)

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Abstract

The study about the validity and clinical usefulness of
the Korean version of the Mini-Mental State

Examination-2

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The Mini-Mental State Examination, 2nd edition (MMSE-2) (Folstein et al., 2010) is developed to secure the disadvantages of the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the one of the most widely used cognitive screening test in clinical trials, including the story memory test that allows more detailed evaluation of verbal memory

than the MMSE, and the processing speed test that can measure the executive function of the frontal lobe. Therefore, it is expected to be more sensitive than the MMSE in discriminating patients with MCI or early stage of dementia. The purpose of this study is to investigate the reliability and validity of the MMSE-2 by translating into Korean and also to investigate the usefulness of the MMSE-2 in Korea through five studies.

In study 1, the MMSE-2 developed by Folstein et al. (2010) was translated into Korean and then investigated the reliability and validity of the MMSE-2 whether this test is reliable in distinguishing between healthy older adults and patients with MCI or AD. The results showed that the MMSE-2 can be used as a valid and reliable screening measure for assessing cognitive impairment in clinical settings in a Korean population, but its ability to distinguish patients with MCI from healthy older adults may not be as highly sensitive as expected.

In study 2, based on the results of the study 1, the usefulness of the MMSE-2 and the K-MMSE (Korean version of the Mini-Mental State Examination) (Kang et al., 1997) was compared to determine which test

is more sensitive in discriminating between healthy older adults and patients with MCI or AD. The results showed that the MMSE-2:SV (MMSE-2:Standard version) and MMSE-2:EV (MMSE-2:Expanded version) were more sensitive and accurate to detect early cognitive decline than the K-MMSE or the MMSE-2:BV (MMSE-2:Brief version), but as the dementia progressed, the K-MMSE or the MMSE-2:BV might be more useful for group discrimination than the MMSE-2:SV and the MMSE-2:EV. Thus, the MMSE-2 appears to be more useful as a cognitive screening test in clinical settings than the K-MMSE.

In study 3, by using brain MRI, the results of the K-MMSE and the MMSE-2 and brain atrophy in healthy older adults, patients with MCI, and patients with AD were compared. In particular, the relationship between various variables of each test and the areas with brain atrophy would be investigated. Moreover, the brain area associated with the newly added story memory test and processing speed test in the MMSE-2 would be examined. The results showed that the MMSE-2 was more related to the degree of atrophy of the general brain area than to the K-MMSE. In particular, the MMSE-2:EV can be more useful as a

cognitive screening test in clinical settings because the MMSE-2:EV has the highest correlation with overall brain area and can measure the frontal lobe function which cannot be measured by the K-MMSE.

In study 4, the reliability and validity of the MMSE-2 was investigated whether this test is reliable in distinguishing between healthy older adults and patients with VaMCI or VD. The results showed that as in the study 1, the MMSE-2 is also found to be clinically useful in distinguishing patients with vascular cognitive impairment (VCI) from those of healthy older adults with high validity and reliability.

Finally, in study 5, based on the results of study 4, the usefulness of the MMSE-2 and the K-MMSE was compared to determine which test is more sensitive in discriminating between healthy older adults and patients with VaMCI or VD. The results showed that as in the study 2, when discriminating between healthy older adults and the group of the patients with VCI, the MMSE-2:SV and the MMSE-2:EV were more sensitive and accurate to detect early cognitive decline than the K-MMSE or the MMSE-2:BV, but as the dementia progressed, the K-

MMSE or the MMSE-2:BV might be more useful than the MMSE-2:SV and the MMSE-2:EV. Therefore, the MMSE-2 can be useful as a cognitive screening test for measuring cognitive function of patients in clinical settings not only for the patients with AD but also for the patients with VCI.

Through this present study, we showed that the newly developed MMSE-2 (Folstein et al., 2010) is more sensitive and clinically useful for differentiating patients with MCI or early stage of dementia from healthy older adults than the MMSE. Therefore, if the MMSE-2 is widely used as a primary cognitive screening test in primary hospitals, public health centers, and elderly welfare centers, it is expected that it will be helpful for early detection of dementia.

Keywords: MMSE, MMSE-2, K-MMSE, Mild cognitive impairment, Alzheimer's disease, Vascular mild cognitive impairment, Vascular dementia

Student Number: 2015-30006

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Introduction

It is a worldwide trend that the proportion of elderly people aged 65 and older has raised significantly since the middle of the 20th century. In particular, the speed of the aging population and low birth rate in Korea has been increased, so an extension of the average life expectancy has also shown that fast compared to other countries. Our country has entered an aging society since 2000, and the elderly population is expected to enter the aging society with a population of over 20% by 2026, and also the number of elderly people aged 65 and older is expected to account for more than 34% of the total population in 2050. This increase in the elderly population is raising awareness that the support of the elderly is not only the responsibility of the family but also the responsibility of the family and society, but the proportion of elderly people aged 65 and older who prepares themselves for their own retirement life has grown by 35% in 2007 to 47.1% in 2011 (National Statistical Office, 2013).

As an aged society, the economic problems of the elderly are also worrisome, but the biggest concern is the health of the elderly. In particular, about 59% of the elderly have said that the most worrisome disease is dementia (Tomato News, 2013). According to the result about studying for senior citizens aged 60 and older, more than half have believed that they had severe memory loss (Zarit, et al., 1981).

As of 2012, the prevalence of dementia in Korea over the aged of 65 elderly was able to 9.18% which was estimated as 541 thousand people (156 thousand of men, 385 thousand of women). Moreover, the prevalence of dementia was expected to about 54 million people in 2012, continue to raise approximately 1.27 million people in 2030, and expect to increase approximately 2.71 million people that will be doubled every 20 years.

Among the total number of patients with dementia, they were account for 71.3% of Alzheimer's disease (AD), 16.9% of vascular dementia (VD), and 11.8% of the other types of dementia. In addition, the number of patients suffering from mild cognitive impairment (MCI)

in 2012 was estimated to exceed 27.82% of the total population aged 65 and older (Department of health and human services, 2013).

Dementia is defined as disability in three or more areas of cognitive function such as memory, language, visuospatial function, computational skills, conceptual or semantic knowledge, executive function, personality or social behavior, and emotional understanding or ability to express which lead to a severe disability in social and occupational functioning (Cummings, et al., 1992). In the following, the high prevalence kinds of dementia in Korea such as MCI, AD, vascular mild cognitive impairment (VaMCI), and VD will be investigated in more detail.

Mild Cognitive Impairment (MCI)

Mild Cognitive Impairment (MCI) could be a previous stage of dementia, which is that although the deterioration of the cognitive function is beyond the scope of normal range, the function of daily life activity or the functional activity is relatively preserved that is not

reasonable in diagnosing as dementia (Petersen et al., 1999). Initially, when making the diagnosis as MCI, a common standard is presented, and it is thought to be as the previous stage of AD so the criteria about amnesic MCI is presented. However, some of patients with MCI feel that cognitive impairment is remained at the same level over time or rather improve so they think that patients with MCI have not thought to be as a homogeneous group. Therefore, patients with MCI have been classified into three different types of group in recent years (Petersen, 2003).

In the first type of MCI, memory impairment is the main symptom which is that even though the memory impairment is shown but other cognitive functions are relatively preserved when compared with age on the neuropsychological tests and it refers to maintaining a relatively normal life.

The second type is multiple domain of MCI which is that even though two or more cognitive disorders are shown on the neuropsychological tests, but a condition is not severe enough to diagnosis as dementia (Lopez et al., 2003).

The third type is non-memory domain of MCI which is that even though one of the cognitive functions (ex., frontal lobe function, language function, or visuospatial function etc.) other than memory is impaired on the neuropsychological tests, there is no problem in everyday life.

In recent years, according to clinical findings, patients with MCI can be classified into various types, and it helps to predict what kinds of dementia will progress in the future.

In the case of amnesic type of MCI, this is the initial state of AD which is one of a degenerative disease, and it is most likely to progress to AD (Palmer et al., 2008). Other types of MCI are considered to be based on vascular, metabolic, and traumatic (Kim et al., 2011),

Recently, the degree of brain atrophy in patients with MCI has been examined via the nerve radiological studies. When the size of the hippocampus of patients with MCI was measured using magnetic resonance imaging (MRI), the size of the hippocampus of patients with MCI who progressed to dementia was less than patients with MCI who

did not progress to dementia (Kaye et al., 1997). Moreover, a comparison of the hippocampus and enthorinal cortex of healthy older adults, patients with MCI and AD showed that there was a significant difference between the two regions in each group (Xu et al., 2000). In other words, the size of the hippocampus gradually decreases as the disorder progresses from mild cognitive impairment to dementia, and this suggests that the memory capacity gradually decreases.

Alzheimer's disease (AD)

Alzheimer's disease (AD) is one of the most common dementia diseases occurring in old age. AD is a neurodegenerative disease, which is caused by gradual loss of cerebral cortical cells, resulting in impairment of memory and general cognitive functions (language, executive function, visual composition, calculation ability etc.), and behavioral disorders and personality changes also occur which lead to impossible to live independently (Morris, 1999). In the early stage of AD,

the ability of memory and visuospatial function has been reduced, and then gradually the ability of praxis, calculation, and executive function has been deteriorated, resulting in personality changes and behavioral disorders.

The most widely used diagnostic criteria for AD are DSM-V (Diagnostic and Statistical Manual of Mental Disorders, Fifth edition) (American Psychiatric Association, 2013) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease & Related Disorders Association) (McKhann et al., 1984). However, the preceding diagnostic criteria was less sensitive to early stage of AD so it was revised to "revising the NINCDS-ADRDA" diagnostic criteria, including biologic indices, for the early diagnosis of AD (Dubois et al., 2007). According to the diagnostic criteria, there is atrophy of the hippocampus, enthorinal cortex, and amygdala in the characteristic features using brain magnetic resonance imaging (MRI), and the characteristic features of functional neuroimaging using positron emission tomography (PET) are decreased glucose metabolism in the bilateral temporo-parietal areas.

Using functional magnetic resonance imaging (fMRI), as a result of comparing the brain functions of patients with AD and the healthy older adults, it was found that the functional connections between the hippocampus and the cortex, hippocampus and subcortical region were widely observed in patients with AD, and the damage of connection between the hippocampus and frontal lobe was also observed (Allen et al., 2007). This suggests that the deterioration of memory function from the initial symptoms of patients with AD is associated with a decrease in the circuit function of the hippocampus and the frontal lobe as well as the functional deterioration of the hippocampus.

Vascular Mild Cognitive Impairment (VaMCI)

Vascular cognitive impairment (VCI) refers to all cognitive dysfunctions caused by cerebrovascular disease (Hachinski et al., 1993). VCI has various forms of cognitive dysfunctions due to vascular dementia and cerebrovascular disease, but it also includes vascular mild cognitive impairment (VaMCI) which describes an abnormal condition

caused by vascular disease and in which a patient presents with cognitive deficits not severe enough to fit the criteria for dementia. Especially, VaMCI is characterized by a decrease in the function of the frontal lobe among the cognitive domains (Gorelick et al., 2011). According to the criteria of AHA/ASA (American Heart Association–American Stroke Association) (Gorelick et al., 2011), VaMCI includes the four types of MCI such as amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain. Moreover, there is a clear temporal relationship between a vascular event and onset of cognitive deficits, and also there is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology.

Vascular Dementia (VD)

Vascular dementia (VD) is defined as the occurrence of dementia due to the development of cerebrovascular disease lesions in the main cerebral cortex involved in cognitive function including memory and

behavioral regulation (Romàn et al., 2002c). VD refers to dementia that occurs in a variety of pathologies, from aortic rupture to small vessel disease, rather than a single disease (Loeb et al., 1996). Thus, unlike AD, it is a heterogeneous group and has many subtypes. The subtypes of vascular disorders are divided into multi-infarct dementia, strategic single-infarct dementia, and small-vessel disease dementia (O'Brien et al., 2003). Multi-infarct dementia is mainly an ischemic stroke caused by stenosis or blockage of major blood vessels such as carotid artery or middle cerebral artery, cardioembolism or hypoperfusion. Cognitive dysfunction is caused by multiple damages of cerebral cortex, which leads to dementia. Strategic infarct dementia, unlike multi-infarct dementia, can present with a single localized cerebral infarction and can cause dementia due to different cognitive dysfunctions depending on the location of cerebral infarction. Subcortical vascular dementia may damage the prefrontal subcortical circuit or thalamo-cortical circuit due to multiple subcortical lacunes or white matter changes in the subcortical region (Romàn et al., 2002; Duering et al., 2011). In particular, McPherson et al. (1996) reported that dementia due to small

vessel disease in the subcortical region of vascular dementia is associated with a higher prevalence among vascular dementia. Among the various kinds of diagnostic criteria for vascular dementia, NINCDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'enseignement en Neurosciences) (Román et al., 1993) is the most stringent and widely used in the world.

Neuropsychological Tests

Measuring the overall cognitive function of patients with dementia by neuropsychological assessments is helpful in diagnosis and treatment. Therefore, it is important to evaluate the cognitive function of patients with dementia by selecting neuropsychological tests that can sensitively discriminate cognitive function changes in patients with dementia.

Neuropsychological evaluation is the evaluation of human general cognitive functions, such as memory, language ability, visuospatial

function, executive function, and behavioral pattern. Through these tests, it is possible to know which area of the brain of patients with dementia is damaged according to the cognitive dysfunction, and also the prognosis is assessed by grasping the problems experience in daily life due to the deterioration of cognitive function so this information helps to diagnose and treat patient's illness. Moreover, it has been proved that the cognitive impairment of patients with dementia is measured sensitively through the neuropsychological tests (Petersen et al., 2001).

As mentioned above, it is essential to evaluate the cognitive function of patients with dementia, since dementia is a disease that affects daily life because of various cognitive dysfunctions including memory. These cognitive deficits should be assessed through a cognitive state assessment, such as a clinical assessment scale or a neuropsychological test. In addition, the recently published revised NINCDS-ADRDA (Dubois et al., 2007), which is a diagnostic criteria for AD, also requires neuropsychological assessments to identify dementia.

In the neuropsychological assessments which measure cognitive function of patients with dementia, there are a comprehensive test battery that evaluates various cognitive domains in detail and a screening test that is used when it is easy to detect dementia in a short time. A comprehensive test battery has the advantage of accurately assessing the degree of disability in the cognitive function by evaluating various cognitive domains in detail. However, it is used in limited clinical settings because it is very important the cooperation of patients because of the long time evaluation and also expert knowledge is needed to interpret the results. On the other hand, a cognitive screening test has a limited amount of information that can be provided compared to a comprehensive test battery, but it can be applied in a short time and can be applied to patients with severe cognitive impairment. Moreover, it has been used in various fields such as public health centers and senior welfare institutions for the elderly as well as hospitals (Park, 2004). In the following, there is a review about the MMSE (Folstein et al., 1975) which has been most widely used as a cognitive screening test in both domestically and

internationally and the MMSE-2 (Folstein et al., 2010) which is recently developed as a cognitive screening test.

1. Mini-Mental State Examination (Folstein et al., 1975)

The MMSE (Folstein et al., 1975) is the most widely used cognitive screening test among the various cognitive screening tools in the world. The MMSE is a simple cognitive screening test that can evaluate the cognitive functions in a short time. The total score is 30 points, and six cognitive areas are evaluated for about 5–10 minutes. The six cognitive domains to be evaluated in the MMSE include time and place orientation, 3 words immediate recall, attention & calculation, 3 words delayed recall, language, and praxis.

The several previous studies reported that the MMSE has been proved to be reliable and valid as a detection test for dementia, and it had relatively high sensitivity and specificity (Folstein et al., 1975; Engedal et al., 1988; O'Connor et al., 1989; Tombaugh et al., 1992; Kaszniak et al., 1986). The MMSE was highly correlated with other

neuropsychological tests (Dick et al., 1984; Kartzman et al., 1983; Thal et al., 1986; Fillenbaum et al., 1987) and had a high correlation (0.73) with the density of synapses in the medial frontal region of the brain (Terry et al., 1991). The MMSE has been proved to be useful in detecting patients with mild to moderate stages of dementia (Kaszniak et al., 1986) and in measuring the cognitive abilities in patients with brain damage (Uhlmann et al., 1991), and also it has been reported to be useful in assessing diagnosis and prognosis (Tasia et al., 1979). Moreover, it has been reported that continuous evaluation over time was possible by using the MMSE (Wieslaw et al., 1993).

In Korea, the MMSE has been developed in various types of Korean versions such as the Korean version of Mini-Mental State Examination (MMSE-K) (Kwon et al., 1989), the Korean version of the Mini-Mental State Examination (K-MMSE) (Kang et al., 1997), and Mini-Mental State Examination in the Korean version of the CERAD assessment packet (MMSE-KC) (Lee et al., 2002), so these tests have been widely used in clinical settings and in local communities including public health centers. Moreover, these Korean versions of the MMSE have been actively used

in domestic epidemiologic studies about the prevalence and diagnosis of dementia (Korean Association for Geriatric Psychiatry, 2003). In addition, large-scale normative data for Korean were also presented, proving the validity and usefulness of the Korean versions of MMSE (Kwon et al., 1989; Lee et al., 2002; Kang et al., 2006)

According to the results of the standardization study and the sensitivity and specificity of the K-MMSE with patients with AD, VD, and Parkinson's disease, 67 (sensitivity = 82.7%) out of 81 patients with AD and 45 (sensitivity = 70.3%) out of 64 patients with VD were detected and the specificity was 91.3%. However, the K-MMSE is a useful screening tool to detect patients with moderate to severe stage of dementia but has not been able to detect patients with early stage of dementia (Kang et al., 1997).

However, previous studies have shown some limitations of the MMSE. The MMSE was influenced by age, culture, and language differences, and there was lack of items to assess executive function of the frontal lobe, so that fronto-temporal dementia or vascular dementia could not be accurately identified. Moreover, the range of test difficulty was

narrow, indicating that there was a limit in distinguishing early stage of dementia from normal cognitive aging (Galasko et al., 1994; Tangalos et al., 1996; Romàn et al., 1993; Mungas et al., 2000; Kang et al., 1997). According to a study by Mungas et al. (2000), the tests used to assess overall cognitive function, such as the MMSE, had nonlinear characteristics that were not sensitive to changes in capability at high and low functional levels. Therefore, the MMSE was not sensitive to detecting early stage of dementia or measuring changes in severe stage of dementia levels due to ceiling effect and floor effect. Moreover, Nelson et al. (1986) reported that the MMSE was focused on verbal items which were not sensitive to impairment of right hemisphere, and also it was easy to produce false positive due to the ceiling effect of people with good cognitive function because of the low difficulty of the items. Srikanth et al. (2006) also showed that the MMSE was not sensitive enough to detect cognitive impairment after stroke, with a sensitivity of 50% and a specificity of 95%. In addition, a study by Scazufca et al. (2008) found that studies of community members with

low socioeconomic status indicated the validity of the MMSE was very limited.

In summary, the MMSE is a useful tool for detecting severe stage of dementia, but it has limitations in distinguishing patients with mild cognitive impairment or early stage of dementia because of the limited range of difficulty, and there is a disadvantage in that there is limited item to measure the executive function of the frontal lobe (Galasko et al., 1994; Kang et al., 1997). Thus, patients with MCI or those with early stage of dementia may be judged to be negative during the primary screening tests. On the following, there is a review of the MMSE-2 (Folstein et al., 2010), which has been made to complement these shortcomings of the MMSE.

2. Mini-Mental State Examination, 2nd edition (Folstein et al., 2010)

The MMSE has a limited validity, does not have the ability to differentiate between patients with MCI or early stage of dementia, and does not have an item to evaluate the frontal function. Moreover, among the items of the MMSE, there are items that are difficult to translate and use in other languages, so they cannot use the same test globally. To overcome these shortcomings, Folstein et al. (2010) developed the MMSE-2 as a cognitive screening test. Unlike the MMSE, the MMSE-2 is composed of two alternative forms (red form & blue form) with the same format to reduce the learning effect that can occur when the same test is performed several times. In addition, MMSE-2 is largely divided into three parts.

The first is the MMSE-2: Brief version (MMSE-2:BV), which is simpler than the MMSE. This test is a total of 16 points, which is a simpler test than the MMSE and is intended to be used in clinical epidemiological studies or in the clinical field. This test includes registration, orientation to time, orientation to place, and recall in sequence. Folstein et al. (2010) reported that among the items in the

MMSE, the previous four tests had reasonable validity and specificity for detecting dementia.

The second is the MMSE-2:Standard version (MMSE-2:SV), which preserves the existing MMSE structure and scoring system. In the MMSE-2:SV, the order of some items in the test has been replaced when compared with the MMSE, and also some of items have been modified and developed, but the total score is 30, and the overall composition is the same as the MMSE.

The third test is the MMSE-2:Expanded version (MMSE-2:EV), which adds two new tests such as story memory and processing speed with a total score of 90 points. The MMSE-2:EV is developed to be more clinically useful than the MMSE. It is expected that it will be more sensitive to discriminate patients with early stage of dementia or MCI by reducing the ceiling effect, increasing the range of origin points, and increasing the range of difficulty than the MMSE. The following is a detailed description about the items of the MMSE-2.

2.1. MMSE-2:BV

The MMSE-2:BV is comprised of four items: registration (3 points), orientation to time (5 points), orientation to place (5 points), and recall (3 points). In order to increase the difficulty of the test, the three words used in the MMSE-2 are one noun word (red form: egg, blue form: milk), one adjective word (red form: confident, blue form: sensible), and one adverb word (red form: after, blue form: before). These words have been syntactically diverse and have been chosen from familiar words in global languages (Folstein et al., 2010). Orientation of time and place are the same as the MMSE.

2.2. MMSE-2:SV

The MMSE-2:SV is comprised of seven items: registration (3 points), orientation to time (5 points), orientation to place (5 points), recall (3 points), attention and calculation (5 points), language (8 points), and drawing (1 points). The total possible score on the MMSE-2:SV is 30 points which is the same as the total score on the MMSE. The overall

item is the same as the MMSE, but there is a modified part of the content. The revised tests are as follows.

First, 'Naming' item used in the K-MMSE has been modified. In the K-MMSE, 'Pen' and 'Watch' were used. However, there is a disadvantage that an examiner cannot carry these things all the time, so a patient is asked to ask for the body part of an examiner (red form: mouth, nose; blue form: eye, ear).

Second, the 'Repetition' item used in the MMSE has been modified. The sentence used in the 'Repetition' item of the MMSE was 'No ifs, ands, or buts', which was difficult to translate into other language so this item was modified to suit the circumstances in each country. For example, in the K-MMSE test, '백문이 불여일견' was used. One of the purposes of developing the MMSE-2 is to use the same test globally so the sentences in the MMSE-2 that can be easily translated into other languages are used. The sentence used in the red form is 'It is a

lovely, cool day but too windy', and the sentence used in the blue form is 'It is a lovely, sunny day but too warm.'

The third revised item is 'Comprehension test.' The 'Comprehension test' used in the MMSE was 'Take this piece of paper, fold it in half, and put it on the floor'. In this test, patients without physical problems can easily act, but patients who are physically paralyzed or who do not move their hands may not be able to perform well, even though they can understand. To make up for this, in the MMSE-2, a picture with one triangle, one circle, and one square is shown in front of a patient, and then a patient is instructed to point the shapes in the order that an examiner spoke. In the red form, the instruction sentence is 'Point to the triangle, then point to the square, then point to the circle.' In the blue form, the instruction sentence is 'Point to the circle, then point to the square, then point to the triangle.'

Finally, a sentence is added in the 'Reading' section. Since the MMSE-2 test has two forms (red form and blue form) unlike the MMSE, 'Close your eyes' in the MMSE is used as it is in red form, 'Open your mouth' is used in blue form. The remaining items (writing and drawing) are used without modification.

2.3. MMSE-2:EV

The MMSE-2:EV includes two new tests such as story memory (25 points) and processing speed (35 points) with the MMSE-2:SV and the total score is 90 points. Folstein et al. (2010) added the story memory test as a test to assess verbal memory which is useful in discriminating patients with MCI or early stage of dementia from healthy older adults. The previous studies have suggested that the story memory test is an important tool for measuring the verbal memory of patients with AD (Butters et al., 1987; Storandt et al., 1984). In addition, it includes the

processing speed test which can evaluate the psychomotor speed of the frontal lobe function.

There are two stories (red and blue forms) used in the story memory test, each consisting of four sentences, and the level of difficulty of sentences is the sixth grade of elementary school. The number of words in the story memory test used in red form is 62, and the number of words in the story memory test used in blue form is 66. Both stories are written in the past tense, using active voice, and possibly made without repeating phrases or words. Folstein et al. (2010) included the story memory test as a verbal memory test because it was important to assess verbal memory in detail to distinguish between healthy older adults and patients with MCI or early stage of dementia. In the previous studies, the verbal memory tasks were the most useful tests in discriminating cognitive functions in patients with early stage dementia and healthy older adults (Eslinger et al., 1994; Jones et al., 1992). Moreover, the story memory test was the most useful test to distinguish between those who develop dementia and those who do not (Christensen et al., 1997), and the first deterioration of the

performance of patients with early stage of dementia was detected in the story memory test among the various types of verbal memory tests (Morris et al., 1991). Therefore, it can be predicted that the story memory test is sensitive to evaluate verbal memory, so that it can discriminate between healthy older adults and patients with MCI or early stage of AD more accurately.

The processing speed test is a test which measures the psychomotor speed and visual searching and attention ability related to the executive function of the frontal lobe (Folstein et al., 2010). Processing speed test is similar to the symbol digit modality test (SDMT: Smith, 1982). In the fMRI study, 18 normal subjects were examined for their relationship to the brain area associated with SDMT, the fronto-parieto-occipital network, caudate nucleus, and cerebellum were activated (Forn et al., 2009).

In recent years, the MMSE-2 (Folstein et al., 2010) is developed to secure the disadvantages of the MMSE, including the story memory test that allows more detailed evaluation of verbal memory than the MMSE and the processing speed test that can measure executive function of

the frontal lobe, so it is expected to be more sensitive than the MMSE in discriminating patients with MCI or early stage of dementia.

Therefore, the purpose of this study is to investigate the reliability and validity of the MMSE-2 by translating into Korean and also to measure the usefulness of the MMSE-2 in Korea through five studies.

In study 1, the MMSE-2 developed by Folstein et al. (2010) is translated into Korean, and then it is investigated the reliability and validity of the MMSE-2 whether this test is reliable in distinguishing between healthy older adults and patients with MCI or AD.

In study 2, based on the results of study 1, the purpose of this study is to compare the usefulness of the MMSE-2 and the K-MMSE to determine which test is more sensitive in discriminating between healthy normal adults and patients with MCI or AD.

In study 3, by using brain MRI, the results of K-MMSE and MMSE-2 and brain atrophy in healthy older adults, patients with MCI, and patients with AD are compared. In particular, the relationship between various variables of each test and the areas with brain atrophy will be investigated. Moreover, the brain area associated with the newly added

story memory test and processing speed test in the MMSE-2 will be evaluated.

In study 4, the processing speed test which measures executive function of the frontal lobe, and the story memory test which measures verbal memory in detail are added in the MMSE-2. Therefore, patients with early stage of VD who are difficult to distinguish from the MMSE will be able to discriminate more sensitively. Thus, the purpose of this study is to evaluate the reliability and validity of the MMSE-2 whether this test is reliable in distinguishing between healthy older adults and patients with VaMCI or VD.

Finally, in study 5, based on the results of study 4, the purpose of this study is to compare the usefulness of the MMSE-2 and the K-MMSE to determine which test is more sensitive in discriminating between healthy older adults and patients with VaMCI or VD.

Study 1

The Validity and Reliability of the Mini-Mental State Examination-2 for Detecting Mild Cognitive Impairment and Alzheimer's Disease in a Korean Population

Introduction

The dementia prevalence rate among elderly people is rapidly increasing as the general population of most countries age. Early detection is the best way to treat dementia and to plan healthcare. Although the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) criteria (American Psychiatric Association, 2013) are used for the diagnosis of dementia, screening tests can identify patients at risk.

The Mini-Mental State Examination (MMSE) is the one of the most widely used screening tests in clinical trials and in general practice to detect cognitive impairment in older adults (Folstein et al., 1975; Lezak

et al., 2004). The MMSE is a quick and easy measure that assesses seven areas of cognitive functioning, and it was shown to have both good test-retest reliability (0.80–0.95) (Folstein et al., 1975; Lezak et al., 2004; O'Connor et al., 1989; Tombaugh et al., 1992) and acceptable sensitivity and specificity to detect mild to moderate stages of dementia (Folstein et al., 1975; Lezak et al., 2004; O'Connor et al., 1989; Tombaugh et al., 1992; Bondi et al., 1996; Engedal et al., 1998). However, the MMSE is less sensitive in detecting patients with MCI and those in the early stages of dementia, and it is also insensitive to impairments in executive functioning, abstract reasoning, and visual perception/construction (Galasko et al., 1994; Kang et al., 1997; Nys et al., 2005). Moreover, false-positive errors might be more common among patients with less education and of lower socioeconomic status, and a ceiling effect might be more common among patients with a high level of education and patients with MCI because of the low level of item difficulty (Nelson et al., 1986). Furthermore, some items in the MMSE were difficult to translate into another language, so they have been adjusted to accommodate the culture of each country.

These limitations led to the development of the Mini-Mental State Examination, 2nd edition (MMSE-2) (Folstein et al., 2010) as a reliable cognitive screening measure to provide finer discrimination. First, there are equivalent, alternative forms of each MMSE-2 version (red and blue forms) to decrease the possibility of practice effects that can occur over serial examinations. The equivalency of the alternative MMSE-2 forms was 0.96 (Folstein et al., 2010). Moreover, unlike the MMSE, there are three different versions of the MMSE-2: the MMSE-2: Brief Version (MMSE-2:BV), which is a shortened version of the MMSE; the MMSE-2: Standard Version (MMSE-2:SV), which is equivalent to the MMSE; and the MMSE-2: Expanded version (MMSE-2:EV), which is slightly longer than the MMSE, is more sensitive to changes with aging and has a ceiling effect.

The total score of the MMSE-2: BV is 16 points. This test is simpler than the MMSE, and it is used to conduct a rapid clinical assessment and to screen larger populations. The MMSE-2:BV is comprised of four items: registration, orientation to time, orientation to place, and recall. According to Folstein et al. (2010), these four items have adequate

sensitivity and specificity to detect the cognitive decline of patients with dementia.

The total possible score on the MMSE-2:SV, is 30 points, which is the same as the total score on the MMSE. The structure of the MMSE was maintained, but some items from the MMSE were changed. Among them, some items that were hard to translate into other languages were changed, and some items were replaced to increase the degree of difficulty of the MMSE-2.

Finally, the total score of the MMSE-2:EV is 90 points because two more items (story memory and processing speed) were added to increase the clinical utility of the MMSE by extending a ceiling effect and to increase the sensitivity and specificity of this version to detect cognitive impairment not only in patients with Alzheimer's disease (AD) but also in patients with subcortical dementia. The story memory item evaluates verbal explicit learning and verbal free recall, and the processing speed test (symbol-digit-coding test) measures psychomotor ability and incidental learning primarily associated with the executive function of the frontal lobe (Folstein et al., 2010).

According to the result of the study on the MMSE-2 (Folstein et al., 2010), the sensitivities of the MMSE-2:SV and the MMSE-2:EV were both 84% for discriminating patients with AD from healthy older adults. Moreover, the sensitivities of the MMSE-2:SV and the MMSE-2:EV were 72% and 75% for discriminating patients with subcortical dementia from normal cognitive aging. That is, the MMSE-2 is a more useful screening measure for dementia and cognitive impairment than the MMSE.

Therefore, the purpose of this study is to evaluate the validity and reliability of the MMSE-2 for assessing patients with MCI and AD in a Korean population. Specifically, we would like to focus on the usefulness of the MMSE-2 as a sensitive screening measure for detecting early cognitive change, which has not been detectable via the MMSE.

Materials and Methods

1. Participants

1.1. Patients

Between June 2012 and April 2013, 323 outpatients and inpatients at the Clinical Neuroscience Center at the Seoul National University Bundang Hospital who complained of memory disturbance or a decline in cognitive functioning underwent a medical examination via an interview, a neurological examination, blood tests, brain imaging with CT or MRI, and neuropsychological assessments to obtain a diagnosis. Among them, 226 patients (90 male, 136 female) were diagnosed with MCI, and 97 patients (36 male, 61 female) were diagnosed with AD. All patients were over 50 years old.

The patients with MCI were diagnosed according to Petersen's criteria (Petersen et al., 2001), and the patients with AD were diagnosed with 'probable AD' based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Associations (NINCDS-

ADRDA) (McKhann et al., 1984). Moreover, based on the Clinical Dementia Rating (CDR) (Morris, 1993) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) (O'Bryant et al., 2008; O'Bryant et al., 2010) scores, patients were classified as having MCI (CDR 0.5, CDR-SOB 0.5-2.5), early stage of AD (CDR 0.5, CDR-SOB 3.0-4.0), mild stage of AD (CDR 1, CDR-SOB 4.5-9.0), or moderate stage of AD (CDR 2, CDR-SOB 9.5-15.5).

1.2. Control participants

Between June 2012 and April 2013, 91 healthy adults who were all over 50 years of old age participated in this study. They were either the caregivers for one of the patients undergoing treatment at Seoul National University Bundang Hospital, or they were recruited from a health care center. They did not have subjective memory complaints, any of 29 exclusionary diseases, or a history suggestive of a decrease in cognitive function (Christensen et al., 1997). They also had scores that were higher than or at most one standard deviation below the mean scores of the respective age- and education-matched population

on the Mini-Mental State Examination in Korea (Kang et al., 1997) and had an average score of 0.42 or lower on the Korean Instrumental Activities of Daily Living (K-IADL) (Kang et al., 2002). This score has been found to discriminate dementia from normal cognitive aging. The K-IADL is an 11-item questionnaire that includes IADLs of shopping, mode of transportation, ability to handle finances, housekeeping, food preparation, ability to use a telephone, taking medication, recent memory, hobbies, watching television, and fixing. All participants were determined to be free of cognitive deficits, and they all consented to participate in this study. Moreover, all participants were free from neurological or psychiatric illnesses, underwent the same neuropsychological assessments as the cognitively impaired subjects and were included in the healthy control group.

2. Instruments

2.1. MMSE-2

The Psychological Association Research (PAR) holds the copyright to the MMSE-2, and they allowed us to translate the MMSE-2 into Korean

before the start of this study. Because one of the purposes of developing the MMSE-2 was to conduct the same test across the world, which the MMSE cannot do, the items of the MMSE-2 should not be modified to adjust to cultural background. Therefore, two neurologists and two neuropsychologists with over ten years of clinical experience translated the MMSE-2 into Korean and then, after performing many stages of modification, sent the back-translated MMSE-2 to PAR for certification. The final version of the MMSE-2 in Korean was modified by experts at PAR, and then the Korean version of the MMSE-2 was finalized in April 2012.

The MMSE-2 is composed of alternative forms, such as the red form and the blue form, to reduce the learning effect that may take place upon repeated use. Moreover, as mentioned earlier, the MMSE-2 has three versions, the MMSE-2:BV, the MMSE-2:SV, and the MMSE-2:EV, and nine subtests of the MMSE-2 are as follows.

The MMSE-2:BV is composed of four subtests in the following order: registration, orientation to time, orientation to place, and recall. The MMSE-2:SV is composed of seven subtests in the following order:

attention and calculation, language, drawing, and the four subtests of the MMSE-2:BV. The MMSE-2:EV is composed of nine subtests in the following order: story memory, processing speed, and the seven subtests of the MMSE-2:SV. The detailed explanation of story memory and processing speed, which are included in the MMSE-2, is as follows.

2.2. Story memory test

The story memory test measures verbal explicit learning and verbal immediate free recall. The story memory test is composed of four sentences, and the sentences are on a sixth grade reading level. The red form and the blue form of the MMSE-2 each contain a different story. The story on the red form was 62 words long, and the story on the blue form was 66 words long. Each story was written in the past tense using the active voice, and contained no repetitive words or phrases (Folstein et al., 2010).

2.3. Processing speed test (Symbol-Digit-Coding test)

The processing speed measure is tapping into frontal lobe areas. This test measures psychomotor ability primarily associated with executive function of the frontal lobe: this is one of the components of the symbol-digit-coding test. Participants are asked to pair symbols with digits within a 30 seconds time limit. Although the stimuli of the red and blue forms are the same, the template that the participants draw is different on each form of the test (Folstein et al., 2010).

2.4. Other neuropsychological assessments

To measure the correlation of the MMSE-2 with other neuropsychological assessments, a variety of cognitive functions, such as attention, verbal memory, visuospatial function ability, executive function, and language function, were measured. Attention was assessed using forward and backward digit span tests (Kang et al., 2002). Verbal memory was assessed using the Seoul Verbal Learning Test (SVLT) (Kang et al., 2003), and a copy of the Rey Complex Figure Test (RCFT) (Meyers et al., 1995) was used to assess visuospatial function. Neuropsychological assessments primarily associated with executive

function, including the Stroop Color-Word Test (Lee et al., 2000), the Semantic Word Fluency Test (SWF) and the Phonemic Word Fluency Test (PWF) (Kang et al., 2000), were used. Naming ability was assessed using the Korean version of the Boston Naming Test (K-BNT) (Kim et al., 1997). Global measurements, including the MMSE in Korean (Kang et al., 1997), CDR (Morris, 1993), and CDR-SOB (O'Bryant et al., 2008; O'Bryant et al., 2010) were also conducted.

3. Procedure

First, to measure the equivalency of the alternative forms of the MMSE-2 tests, 138 patients completed both the red and blue forms of the MMSE-2. To eliminate the order effect, half of the 138 patients completed the red form of the MMSE-2 first and the other half completed the blue form of the MMSE-2 first. According to the result of Pearson's correlation analysis, the correlation coefficient was high between the red and blue forms of the MMSE-2:BV ($r=0.90$, $p<0.001$), the MMSE-2:SV ($r=0.97$, $p<0.001$), and the MMSE-2:EV ($r=0.97$, $p<0.001$).

Therefore, half of the patients who participated in this study completed the red form of the MMSE-2, and the other half of completed the blue form of the MMSE-2. Also, the order in which the neuropsychological assessments were administered is shown in Table 1.

4. Statistical analysis

An analysis of variance (ANOVA) was used to compare age and education levels, and a chi-square test was used to compare gender across all three groups. The results of the neuropsychological tests including the MMSE, among the three groups were analyzed using an analysis of covariance (ANCOVA) after controlling for demographic variables (age and education). Moreover, the MMSE-2 scores of all three groups were analyzed with an ANCOVA followed by Tukey's test for *post-hoc* analysis.

Reliability was assessed through measurements of internal consistency, test-retest reliability, and interrater reliability. The internal consistency of the MMSE-2 was measured using Cronbach's α coefficient. To assess test-retest reliability, the MMSE-2 was re-administered one to

two months (34.48 ± 3.48 days) after the initial test to 16 patients with MCI, 4 patients with AD, and 7 healthy older adults, and the data were analyzed using Pearson's correlation coefficients. Moreover, to assess the equivalency of the blue and red forms of the MMSE-2, 138 participants were given both the blue and red forms in a counterbalanced design, with the second administration immediately following the first, and the data were analyzed using Pearson correlation coefficients. Interrater reliability was calculated between two neuropsychologists ($n=160$) using the intraclass correlation coefficient (ICC).

Finally, the validity of the MMSE-2 was analyzed as follows. To evaluate the construct validity, a Varimax rotated factor analysis was used to explore the factor structure of the 13 items. Moreover, to assess the concurrent validity of the MMSE-2, Pearson's correlation coefficient was used to compare the MMSE-2 with the MMSE, the CDR, the CDR-SOB, SVLT, the copy test of RCFT, the SWF, the PWF, the Stroop Color-Word test, the K-BNT, and the digit span test (forward & backward). To verify the discriminant validity based on the severity of

dementia, all participants were classified into four groups according to CDR and CDR-SOB, and the average scores of the MMSE-2 were compared among these four groups using ANCOVA. To evaluate the diagnostic utility of the MMSE-2, the sensitivity and specificity of the MMSE-2 was examined using a receiver operating characteristics (ROC) curve and area under the curve (AUC) measurements. Data were analyzed using SPSS 18.0. (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be significant for all analyses.

Results

1. The participants' demographic data

The demographic data are presented in Table 2. A total of 414 elderly participants (155 men and 259 women) were enrolled in this study. The mean age of the patients with MCI was 71.05 ± 7.73 years (range: 70–72 years), and the mean age of the patients with AD was 75.38 ± 7.60 (range: 73–77 years). The mean age of the healthy older adults was 67.05 ± 7.55 years (range: 65–69 years). The mean number of years of education was 11.45 ± 4.80 years (range: 10–12 years) in the patients with MCI, 9.63 ± 5.15 years (range: 8–11 years) in the patients with AD, and 10.98 ± 5.21 years (range: 9–12 years) in the healthy older adults.

There was no significant difference in the participants' gender, $\chi^2(1, 414) = 1.76$, $p = 0.42$, but there were significant differences in age, $F(2, 411) = 27.82$, $p < 0.001$, and education, $F(2, 411) = 4.38$, $p < 0.013$, between the three groups. According to Tukey's *post hoc* analysis, the mean age of the patients with AD was significantly higher than the

mean age of the patients with MCI and of the healthy older adults, and the mean age for the patients with MCI was significantly higher than that of the healthy older adults. Moreover, the mean number of years of education for the patients with MCI was higher than for the patients with AD, and there was no significant difference in the mean number of years of education between the patients with AD and the healthy older adults or between the patients with MCI and the healthy older adults.

2. The results of participants' neuropsychological assessments

The results of the neuropsychological assessments of the three groups (MCI, AD, and healthy older adults) were compared. With respect to each of the cognitive domain scores, the three groups differed significantly in each of the domain assessed: attention, verbal memory, visuospatial function, language function, and frontal/executive function (all $p < 0.05$). Tukey's *post hoc* analysis of the cognitive

domain revealed that the scores of the healthy older adults were significantly higher than the scores of the patients with MCI and AD and that the scores of the patients with MCI were significantly higher than the scores of the patients with AD in the MMSE, the SVLT, the copy of the RCFT, the SWF, the PWF, the Stroop Color-Word test (color naming), the K-BNT, and the digit span test (forward & backward). However, in the Stroop Color-Word test (word reading), although there was no significant difference between the healthy older adults and the patients with MCI, the scores of the two groups (healthy older adults and MCI) were significantly higher than those of the patients with AD. The mean scores of the subtests for each group and the results of Tukey's *post-hoc* analysis are presented in Table 3.

3. MMSE-2

3.1. The equivalency of the blue and red forms of the MMSE-2

The MMSE-2 blue and red forms equating sample consisted of 138 participants with an average age of 72.22 ± 7.46 years and an average educational level of 10.58 ± 5.10 years. The average scores of the

MMSE-2:BV (red and blue forms), MMSE-2:SV (red and blue forms), and MMSE-2:EV (red and blue forms) are presented in Table 4. The reliability was high for all three alternative forms: the MMSE-2:BV ($r = 0.90, p < 0.01$), the MMSE-2:SV ($r = 0.97, p < 0.01$), and MMSE-2:EV ($r = 0.97, p < 0.01$).

3.2. The results of the MMSE-2 in the groups of normal, MCI, and AD

The MMSE-2:BV scores of the participants in the three groups are shown in Table 5. An ANCOVA that controlled for age and education revealed significant differences between the three groups on the MMSE-2:BV. According to Tukey's *post hoc* analyses, the total score of the MMSE-2:BV was significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and it was significantly higher for the patients with MCI than for the patients with AD. Especially, among all items of the MMSE-2, the score of recall was significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and it was significantly higher for

the patients with MCI than for the patients with AD. However, there were no significant differences in the items registration, orientation to time, and orientation to place between the healthy older adults and the patients with MCI, but the scores of the three items in the MMSE-2:BV were significantly higher for the healthy older adults and the patients with MCI than for the patients with AD.

The MMSE-2:SV scores of the participants in the three groups are shown in Table 6. An ANCOVA that controlled for age and education revealed significant differences between the three groups on the MMSE-2:SV. Tukey' s *post hoc* analyses showed that the total score of the MMSE-2:SV was significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and it was also significantly higher for the patients with MCI than for the patients with AD. Particularly, among all MMSE-2 items, the score of recall was significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and it was also significantly higher for the patients with MCI than for the patients with AD. However, there were no significant differences in the items registration,

orientation to time, orientation to place, attention and calculation, language, or drawing between the healthy older adults and the patients with MCI, but the scores of six items on the MMSE-2:SV were significantly higher for the healthy older adults and the patients with MCI than for the patients with AD.

The MMSE-2:EV scores of the participants in the three groups are shown in Table 7. An ANCOVA that controlled for age and education revealed significant differences between the three groups on the MMSE-2:EV. Tukey' s *post hoc* analyses showed that the total score of the MMSE-2:EV was significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and it was also significantly higher for the patients with MCI than for the patients with AD. Particularly, among the MMSE-2:EV items, the scores of recall, story memory, and processing speed were significantly higher for the healthy older adults than for the patients with MCI and the patients with AD, and the scores of three items were also significantly higher for the patients with MCI than for the patients with AD. However, there were no significant differences in the items registration,

orientation to time, orientation to place, attention and calculation, language, or drawing between the healthy older adults and the patients with MCI, but the scores of six items on the MMSE-2:EV were significantly higher for the healthy older adults and the patients with MCI than for the patients with AD.

4. Reliability analyses

4.1. Internal Consistency

The internal reliability (Cronbach's α) of three versions of the MMSE-2 (red and blue forms) among the three groups are presented in Table 8. The interrater reliability was high because alphas ranged from 0.62 to 0.79.

4.2. Test-retest reliability

Sixteen patients with MCI, 4 patients with AD, and 7 healthy older adults were tested twice, at an interval that averaged 34.48 ± 3.48 days, to examine the test-retest reliability. The mean age of the participants

was 68.37 ± 11.17 years and the mean number of years of education was 11.17 ± 3.95 years. The test-retest reliability of three versions of the MMSE-2 was high, ranging from 0.76 to 0.90 (Table 9).

4.3. Interrater reliability

Two trained neuropsychologists were present during the administration of the MMSE-2 to 160 participants. One-way, single-measure intraclass correlation coefficients (ICCs) were calculated for each item of the MMSE-2 (Table 10). The ICCs ranged from 0.94 to 0.99. There was 100% agreement for registration, orientation to time, orientation to place, attention and calculation, naming, repetition, comprehension, reading, writing, drawing, and the psychomotor speed task.

5. Validity analyses

5.1. Construct validity

Construct validity was examined via principal component analysis with Varimax rotation to determine the factor structure of the MMSE-2 in each group. The results of the factor analyses in each group are as follows.

The factor analysis of the healthy older adults identified two factors in the MMSE-2 that explained approximately 48.4% of the total variance, as shown in Table 11. Factor 1 included six subtests (recall, orientation to place, story memory, processing speed, attention and calculation, and orientation to time) that explained 36.0% of the variance. We named this factor as “tests that are sensitive to decline in cognitive functions”. Factor 2 included three subtests (registration, language, and drawing) that explained 12.4% of the variance. We named this factor as “tests that are not sensitive to decline in cognitive functions”.

The factor analysis of the patients with MCI identified three factors in the MMSE-2 that explained approximately 52.2% of the total variance (Table 12). Factor 1 included three subtests (attention and calculation, drawing, and processing speed) that explained 27.5% of the

variance. We named this factor as “tests related with frontal lobe function”. Factor 2 included two subtests (recall and story memory) that explained 13.3% of the variance. We named this factor as “tests related with verbal memory”. Factor 3 included three subtests (orientation to place, orientation to time, and registration) that explained 11.3% of the variance. We named this factor as “tests related with orientation and immediate recall”.

The factor analysis of the patients with AD identified two factors in the MMSE-2 that explained approximately 45.3% of the total variance (Table 13). Factor 1 included five subtests (language, processing speed, drawing, attention and calculation, and registration) that explained 30.2% of the variance. We named this factor as “tests for cognitive domains except for episodic memory”. Factor 2 included four subtests (orientation to time, recall, story memory, and orientation to place) that explained 15.1% of the variance. We named this factor as “tests for episodic memory”.

5.2. Concurrent validity

The concurrent validity of the MMSE-2 was examined through correlation with the values of the MMSE, the CDR, the CDR-SOB, the SVLT, the copy of RCFT, the SWF, the PWF, the Stroop Color-Word test, the K-BNT, and the digit span test (forward & backward). The results showed that the three versions of the MMSE-2 were significantly correlated with the cognitive function tests (Table 14). Particularly, the correlation coefficients were high between the MMSE-2:BV and the MMSE ($r = 0.84$, $p < 0.01$), the MMSE-2:SV and the MMSE ($r = 0.92$, $p < 0.01$), and the MMSE-2:EV and the MMSE ($r = 0.83$, $p < 0.01$).

6. Discriminant validity by CDR stage analysis

To examine the utility of the MMSE-2 to detect dementia severity, the participants were reclassified into five groups according to their CDR and CDR-SOB scores. Specifically, the healthy older adults were assigned a CDR score of 0 (CDR-SOB 0), the patients with MCI were assigned a CDR score of 0.5 (CDR-SOB 0.5-2.5), the patients with early stage of AD were assigned a CDR score of 0.5 (CDR-SOB 3.0-4.0), the

patients with mild stage of AD were assigned a CDR score of 1 (CDR-SOB 4.5–9.0), and the patients with moderate stage of AD were assigned a CDR score of 2 (CDR-SOB 9.5–15.5). The average age, educational level, and gender of the participants are presented in Table 15. Although there was no significant difference in gender, $\chi^2(1,414) = 3.03$, $p = 0.93$, between the five groups, there were significant differences in age, $F(4,409) = 14.703$, $p < 0.001$, and education, $F(4,409) = 2.598$, $p = 0.036$.

The scores of all three versions of the MMSE-2 for the participants in the five groups are presented in Table 16. An ANCOVA that controlled for age and education revealed significant differences between the five groups in all three versions of the MMSE-2. According to Tukey's *post hoc* analyses, the five groups differed significantly with respect to the scores of the MMSE-2:BV and the MMSE-2:SV. However, on the MMSE-2:EV, the three groups (MCI, early stage of AD, and healthy older adults) differed significantly, but there was no significant difference between the patients with mild stage of AD and the patients with moderate stage of AD.

7. Diagnostic utility

To measure the diagnostic utility of the three versions of the MMSE-2, the ROC curve analysis and the area under the curve (AUC) was calculated. The results of each version of the MMSE-2 were as follows.

7.1. MMSE-2:BV

First, for discriminating the healthy older adults from the patients with MCI, the AUC of the MMSE-2:BV was 0.71 (95% confidence interval, CI, 0.64-0.77, $p < 0.001$). The sensitivity of the MMSE-2:BV was 60% and the specificity was 75% when using a cut-off score of ≤ 14 of 16 to predict MCI. Second, for discriminating the patients with MCI from the patients with AD, the AUC of the MMSE-2:BV was 0.93 (95% CI, 0.90-0.96, $p < 0.001$). The sensitivity of the MMSE-2:BV was 88% and the specificity was 87% when using a cut-off score of ≤ 10 of 16 to predict AD. Finally, for discriminating the healthy older adults from the patients with AD, the AUC of the MMSE-2:BV was 0.97 (95% CI, 0.96-0.99, $p < 0.001$). The sensitivity of the MMSE-2:BV was 98%

and the specificity was 70% when using a cut-off score of ≤ 10 of 16 to predict AD (Figure 1).

7.2. MMSE-2:SV

First, for discriminating the healthy older adults from the patients with MCI, the AUC of the MMSE-2: SV was 0.72 (95% CI, 0.66–0.79, $p < 0.001$). The sensitivity of the MMSE-2:SV was 74% and the specificity was 59% when using a cut-off score of ≤ 26 of 30 to predict MCI. Second, for discriminating the patients with MCI from the patients with AD, the AUC of the MMSE-2:SV was 0.93 (95% CI, 0.89–0.96, $p < 0.001$). The sensitivity of the MMSE-2:SV was 84% and the specificity was 87% when using a cut-off score of ≤ 23 of 30 to predict AD. Finally, for discriminating the healthy older adults from the patients with AD, the AUC of the MMSE-2:SV was 0.95 (95% CI, 0.92–0.98, $p < 0.001$). The sensitivity of the MMSE-2:SV was 92% and the specificity was 87% when using a cut-off score of ≤ 23 of 30 to predict AD (Figure 2).

7.3. MMSE-2:EV

First, for discriminating the healthy older adults from the patients with MCI, the AUC of the MMSE-2:EV was 0.73 (95% CI, 0.66–0.80, $p < 0.001$). The sensitivity of the MMSE-2:EV was 71% and the specificity was 69% when using a cut-off score of ≤ 46 of 90 to predict MCI. Second, for discriminating the patients with MCI from the patients with AD, the AUC of the MMSE-2:EV was 0.92 (95% CI, 0.89–0.95, $p < 0.001$). The sensitivity of the MMSE-2:EV was 82% and the specificity was 85% when using a cut-off score of ≤ 36 of 90 to predict AD. Finally, for discriminating the healthy older adults from the patients with AD, the AUC of the MMSE-2:EV was 0.94 (95% CI, 0.91–0.98, $p < 0.001$). The sensitivity of the MMSE-2:EV was 92% and the specificity was 71% when using a cut-off score of ≤ 34 of 90 to predict AD (Figure 3).

Discussion

This study verified the newly developed MMSE-2 as a reliable and valid cognitive screening measure for MCI and AD in a Korean population. The results demonstrated several key points.

First, the results of the MMSE-2 and other neuropsychological assessments that measure attention, verbal memory, visuospatial function, language function, and frontal/executive function significantly differed between the three groups (healthy older adults, MCI, AD).

Second, the MMSE-2 was shown to have good internal consistency, high test-retest reliability, and high inter-rater reliability.

Third, to demonstrate the construct validity of the MMSE-2, a factor analysis was performed on each of the three groups. For the patients with MCI, the MMSE-2 was divided into three factors. The first factor included the tests related to working memory and frontal lobe functioning, such as attention and calculation, drawing, and psychomotor speed task. The drawing test was correlated with temporal elements of working memory, and it had indirect effects on attention and calculation (Shigemori et al., 2010). The second factor included the tests

related to verbal memory, such as recall and story memory tests. The third factor included the tests related to orientation and immediate recall, such as orientation to place, orientation to time, and registration tests. Tests of working memory and verbal memory were sensitive for detecting early decline in cognitive function (Greene et al., 1996; Johnson et al., 1994; Salthouse et al., 1988). Moreover, working memory was related to a decline in episodic memory, and tests of verbal memory measured episodic memory. Thus, the tests related to episodic memory may be sensitive in assessing cognitive functioning of the patients with MCI.

For the patients with AD, the MMSE-2 was divided into two factors. The first factor included language, processing speed, drawing, attention and calculation, and registration, which can measure overall cognitive functioning other than memory. The second factor included the tests related to episodic memory, such as orientation to time, recall, story memory, and orientation to place.

We compared the factor analysis of the patients with AD and that of the patients with MCI. For the patients with MCI, the tests of

orientation to time and orientation to place were not sensitive to changes in cognitive functions, but for the patients with AD, tests of recall and story memory and tests of orientation to time and orientation to place were sensitive to changes in cognitive functions. Therefore, as mild cognitive impairment progresses to AD, tests related to episodic memory seems to become sensitive to changes in cognitive function.

In the healthy older control group, the MMSE-2 was divided into two factors: tests that are sensitive to decline in cognitive functions, such as recall, orientation to place, story memory, processing speed, attention and calculation, and orientation to time orientation; and tests that are not sensitive to decline in cognitive functions, such as registration, language and drawing. Therefore, this demonstrated that the factor analyses differed between the groups based on the degree of cognitive impairment and confirmed that all MMSE-2 items were clearly divided between the groups.

The present study also showed that the MMSE-2 was highly correlated with various neuropsychological assessments with verified validity. Particularly, the MMSE-2 had a very high correlation with the

MMSE, and it also demonstrated a high correlation with verbal memory frontal lobe function tests. Even though there is executive function test in the MMSE such as attention and calculation, the MMSE is insensitive to impairments in executive functioning, abstract reasoning, and visual perception/concentration (Nys et al., 2005). However, the MMSE-2, as Folstein et al. (2010) suggested, has shown its ability to measure executive function in more detail, and thus, it can measure a greater variety of cognitive functions than the MMSE.

Fourth, the scores of the MMSE-2 could also discriminate between each of the CDR and CDR-SOB stages. Thus, the scores of the MMSE-2 declined significantly as CDR and CDR-SOB scores increased, which confirms that the MMSE-2 is able to discriminate between the stages of CDR and CDR-SOB. This showed that the MMSE-2 is a useful instrument as a screening measure for detecting the progress of cognitive impairment. However, with the MMSE-2:EV, there was no significant difference between the patients with mild stage of AD and the patients with moderate stage of AD. One of many possible reasons for this finding is that the difficulty levels of story memory and

processing speed tests might seem too challenging for the patients beyond mild stage of AD, and so a floor effect is highly probable. Thus, the MMSE-2:BV and MMSE-2:SV can be more effective than the MMSE-2:EV in assessing cognitive functions of the patients with mild stage of AD and the patients with moderate stage of AD.

Finally, the sensitivity and specificity of the three versions of the MMSE-2 in discriminating between the healthy older adults and the patients with MCI were tested: for the MMSE-2:BV, the sensitivity was 60% and the specificity was 75% at the cut-off score of 14/15; for the MMSE-2:SV, the sensitivity was 74% and the specificity was 59% at the cut-off score of 26/27; and for the MMSE-2:EV, the sensitivity was 71% and the specificity was 69% at the cut-off score of 46/47. All three versions of the MMSE-2 could similarly discriminate between the two groups.

Moreover, the sensitivity and specificity of the three versions of the MMSE-2 in discriminating between the patients with MCI and the patients with AD were tested: for the MMSE-2:BV, the sensitivity was 88% and the specificity was 87% at the cut-off score of 11/12; for the

MMSE-2:SV, the sensitivity was 84%, and the specificity was 87% at the cut-off score of 23/24; and for the MMSE-2:EV, the sensitivity was 82% and the specificity was 85% at the cut-off score of 36/37. All three versions of the MMSE-2 could similarly discriminate between the two groups.

The sensitivity and specificity of three versions of the MMSE-2 in discriminating between the healthy older adults and the patients with AD were tested: for the MMSE-2:BV, the sensitivity was 98% and the specificity was 70% at the cut-off score of 10/11; for the MMSE-2:SV, the sensitivity was 93%, and the specificity was 80% at the cut-off score of 22/23; and for the MMSE-2:EV, the sensitivity was 92% and the specificity was 71% at the cut-off score of 34/35. All three versions of the MMSE-2 could similarly discriminate between the two groups.

Overall, the MMSE-2 is useful for discriminating between the patients with MCI vs. the patients with AD and between healthy older adults vs. the patients with AD, but its ability to discriminate between the healthy older adults vs. the patients with MCI is less than satisfactory.

Nevertheless, the MMSE-2 is slightly more sensitive in this area than the MMSE, which has sensitivity of 82.7% at the cut-off score of 23/24 [9].

In summary, according to these results, as Folstein et al. (2010) suggested, the MMSE-2 can be used as a valid and reliable screening measure for assessing cognitive impairment in clinical settings in a Korean population, but its ability to distinguish the patients with MCI from healthy older adults may not be as highly sensitive as expected.

Table 1. Order of neuropsychological assessments

Order	List of neuropsychological assessments
1	MMSE-2 (red form or blue form)
2	SVLT-immediate recall
3	RCFT-copy
4	Digit span-forward
5	Digit span-backward
6	Stroop Color-Word test (word reading)
7	Stroop Color-Word test (color naming)
8	SVLT-delayed recall
9	SVLT-recognition
10	SWF-animal
11	SWF-supermarket items
12	PWF-ㄱ/ㅇ/ㄴ
13	K-BNT
14	MMSE

Abbreviations: MMSE-2, Mini-Mental State Examination-2; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; K-BNT, Korean version of Boston Naming Test; MMSE, Korean version of the Mini-Mental State Examination.

Table 2. Characteristics of participants (M±SD)

	All participants (n=414)		
	Normal (n=91)	MCI (n=226)	AD (n=97)
Age (years)	67.05±7.55	71.05±7.73*	75.38±7.60 [†]
Education (years)	10.98±5.21	11.45±4.80	9.63±5.15 [‡]
Male/Female	29/62	90/136	36/61

Abbreviations: M, Mean; SD, Standard deviation; MCI, Mild Cognitive impairment; AD, Alzheimer's disease.

Note.

* $p < 0.001$ for MCI vs. Normal.

[†] $p < 0.001$ for AD vs. MCI and Normal.

[‡] $p < 0.013$ for AD vs. MCI.

Table 3. The results of neuropsychological assessments in the groups of normal, MCI, and AD (M±SD)

Neuropsychological assessments	N(1)	MCI(2)	AD(3)	F	df	Post-hoc
MMSE	27.29±2.31	25.68±2.68	19.33±3.82	201.32*	2, 409	1>2>3
SVLT-immediate recall	21.47±4.06	17.15±4.39	10.91±3.71	111.87*	2, 409	1>2>3
SVLT-delayed recall	7.26±2.00	3.49±2.92	0.29±0.92	152.14*	2, 409	1>2>3
SVLT-recognition	9.46±1.68	7.42±2.42	3.70±2.87	104.73*	2, 409	1>2>3
RCFT-copy	32.41±3.87	28.87±5.32	22.50±7.63	66.91*	2, 403	1>2>3
SWF-animal	17.40±4.14	12.86±3.75	8.84±4.31	80.74*	2, 409	1>2>3
SWF-supermarket items	18.97±5.32	14.46±5.84	8.33±4.57	61.57*	2, 404	1>2>3
PWF-ㄱ, ㅁ, ㄴ	26.35±11.01	20.41±9.78	13.83±8.95	27.51*	2, 358	1>2>3
Stroop Color-Word test (word reading)	110.89±5.98	111.13±4.03	105.31±13.68	13.49*	2, 374	1=2>3
Stroop Color-Word test (color naming)	88.30±17.91	70.41±23.45	40.73±24.30	63.86*	2, 354	1>2>3
K-BNT	48.15±8.09	40.48±9.97	28.70±11.22	63.33*	2, 409	1>2>3
Digit span-forward	6.07±1.51	5.63±1.40	4.91±1.45	6.44*	2, 409	1>2>3
Digit span-backward	4.10±1.15	3.56±0.97	2.92±0.95	25.23*	2, 409	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE, Korean version of the Mini-Mental State Examination; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; K-BNT, Korean version of Boston Naming Test; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.05$.

Table 4. The results of red and blue forms of the three versions of the MMSE-2 ($M \pm SD$)

MMSE-2	Form	M	SD	Alternating forms reliability
Brief Version	Red	12.10	2.896	$r=0.90$
	Blue	11.88	2.891	$(p < 0.01)$
Standard Version	Red	23.91	4.175	$r=0.97$
	Blue	23.82	4.026	$(p < 0.01)$
Expanded Version	Red	39.99	11.136	$r=0.97$
	Blue	41.12	11.488	$(p < 0.01)$

Abbreviations: M, Mean; SD, Standard deviation; MMSE-2, Mini-Mental State Examination-2; r, Pearson's correlation coefficient.

Table 5. The results of the MMSE-2:BV in the groups of normal, MCI, and AD (M \pm SD)

MMSE-2:BV	N(1)	MCI(2)	AD(3)	F	<i>df</i>	η^2	<i>Post-hoc</i>
Registration	2.91 \pm 0.44	2.91 \pm 0.35	2.60 \pm 0.59	12.38*	2, 409	0.18	1=2>3
Orientation to time	4.80 \pm 0.43	4.54 \pm 0.77	2.40 \pm 1.52	175.53*	2, 409	0.39	1=2>3
Orientation to place	4.86 \pm 0.38	4.73 \pm 0.53	3.62 \pm 1.06	91.73*	2, 409	0.38	1=2>3
Recall	1.87 \pm 0.85	1.20 \pm 0.84	0.26 \pm 0.51	77.30*	2, 409	0.27	1>2>3
Total score	14.43 \pm 1.32	13.37 \pm 1.58	8.91 \pm 2.54	230.62*	2, 409	0.55	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.01$.

Table 6. The results of the MMSE-2:SV in the groups of normal, MCI, and AD (M±SD)

MMSE-2:SV	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Registration	2.91±0.44	2.91±0.35	2.60±0.59	12.38*	2, 409	0.18	1=2>3
Orientation to time	4.80±0.43	4.54±0.77	2.40±1.52	175.53*	2, 409	0.39	1=2>3
Orientation to place	4.86±0.38	4.73±0.53	3.62±1.06	91.73*	2, 409	0.38	1=2>3
Recall	1.87±0.85	1.20±0.84	0.26±0.51	77.30*	2, 409	0.27	1>2>3
Attention and Calculation	4.09±1.17	3.77±1.24	2.61±1.56	28.29*	2, 409	0.38	1=2>3
Language	7.69±0.92	7.67±0.57	7.19±1.00	7.94*	2, 409	0.26	1=2>3
Drawing	0.95±0.23	0.90±0.30	0.69±0.47	13.54*	2, 409	0.18	1=2>3
Total Score	27.26±2.66	25.71±2.35	19.39±3.94	205.00*	2, 409	0.69	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:SV, Mini-Mental State Examination-2:Standard Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.01$.

Table 7. The results of the MMSE-2:EV in the groups of normal, MCI, and AD (M \pm SD)

MMSE-2:EV	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Registration	2.91 \pm 0.44	2.91 \pm 0.35	2.60 \pm 0.59	12.38*	2, 409	0.18	1=2>3
Orientation to time	4.80 \pm 0.43	4.54 \pm 0.77	2.40 \pm 1.52	175.53*	2, 409	0.39	1=2>3
Orientation to place	4.86 \pm 0.38	4.73 \pm 0.53	3.62 \pm 1.06	91.73*	2, 409	0.38	1=2>3
Recall	1.87 \pm 0.85	1.20 \pm 0.84	0.26 \pm 0.51	77.30*	2, 409	0.27	1>2>3
Attention and calculation	4.09 \pm 1.17	3.77 \pm 1.24	2.61 \pm 1.56	28.29*	2, 409	0.38	1=2>3
Language	7.69 \pm 0.92	7.67 \pm 0.57	7.19 \pm 1.00	7.94*	2, 409	0.26	1=2>3
Drawing	0.95 \pm 0.23	0.90 \pm 0.30	0.69 \pm 0.47	13.54*	2, 409	0.18	1=2>3
Story memory	10.46 \pm 3.50	7.15 \pm 3.21	3.34 \pm 1.80	109.96*	2, 409	0.46	1>2>3
Processing speed	12.24 \pm 4.31	10.47 \pm 4.03	6.35 \pm 3.40	38.78*	2, 409	0.40	1>2>3
Total Score	49.84 \pm 9.59	43.48 \pm 7.81	29.06 \pm 7.17	168.37*	2, 409	0.69	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:EV, Mini-Mental State Examination-2:Expanded Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.01$.

Table 8. Internal Consistency: MMSE-2:BV, MMSE-2:SV, and MMSE-2:EV (red and blue forms)

MMSE-2	Red form			Blue form		
	N(r)	MCI(r)	AD(r)	N(r)	MCI(r)	AD(r)
BV	0.728	0.730	0.715	0.697	0.718	0.746
SV	0.741	0.665	0.726	0.686	0.676	0.709
EV	0.686	0.698	0.726	0.621	0.668	0.705
Total	0.783	0.747	0.729	0.793	0.751	0.728

Abbreviations: N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2, Mini-Mental State Examination-2; BV, Brief version; SV, Standard version; EV, Expanded version; r, Cronbach's α coefficient.

Table 9. Test-retest reliability of the MMSE-2

MMSE-2	r	<u>1st Test</u>		<u>2nd Test</u>	
		M	SD	M	SD
BV	0.76*	13.48	1.45	13.52	1.55
SV	0.82*	26.04	2.05	26.07	2.15
EV	0.90*	45.67	6.39	44.37	5.87

Abbreviations: M, Mean; SD, Standard deviation; MMSE-2, Mini-Mental State Examination-2; BV, Brief version; SV, Standard version; EV, Expanded version; r, Pearson's correlation coefficient.

Note.

* $p < 0.01$.

Table 10. Interrater reliability of the MMSE-2

MMSE-2	ICC	% agreement
Registration	–	100%
Orientation to time	–	100%
Orientation to place	–	100%
Recall	0.99	
Attention and calculation	–	100%
Naming	–	100%
Repetition	–	100%
Comprehension	–	100%
Reading	–	100%
Writing	–	100%
Drawing	–	100%
Story memory	0.94	
Processing speed	–	100%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; ICC, Intraclass Correlation Coefficient.

Table 11. Factor analysis after Varimax rotation for the healthy older adults group

Variables	Factors	
	1	2
Recall	0.736	-0.021
Orientation to place	0.633	0.076
Story memory	0.628	0.432
Processing speed	0.597	0.496
Attention and calculation	0.574	0.505
Orientation to time	0.560	0.029
Registration	0.105	0.793
Language	0.045	0.657
Drawing	0.060	0.498

Abbreviations: 1, “Tests that are sensitive to decline in cognitive functions”; 2, “Tests that are not sensitive to decline in cognitive functions”.

Table 12. Factor analysis after Varimax rotation for the patients with mild cognitive impairment

Variables	Factors		
	1	2	3
Attention and Calculation	0.766	0.174	-0.228
Drawing	0.643	-0.129	0.306
Processing speed	0.593	0.271	0.325
Language	0.303	0.291	0.131
Recall	-0.018	0.839	0.048
Story memory	0.415	0.669	0.124
Orientation to place	0.099	0.149	0.640
Orientation to time	-0.168	0.404	0.638
Registration	0.242	-0.101	0.574

Abbreviations: 1, “Tests related with frontal lobe function”; 2, “Tests related with verbal memory”; 3, “Tests related with orientation and immediate recall”.

Table 13. Factor analysis after Varimax rotation for the patients with Alzheimer' s disease

Variables	Factors	
	1	2
Language	0.749	0.129
Processing speed	0.718	0.330
Drawing	0.674	-0.219
Attention and Calculation	0.606	0.305
Registration	0.551	-0.036
Orientation to time	0.233	0.780
Recall	-0.175	0.612
Story memory	0.020	0.546
Orientation to place	0.324	0.477

Abbreviations: 1, "Tests for cognitive domains except for verbal memory"; 2, "Tests for episodic memory".

Table 14. Correlation between the MMSE-2 and cognitive measures

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. MMSE-2:BV	1														
2. MMSE-2:SV	0.901*	1													
3. MMSE-2:EV	0.791*	0.875*	1												
4. MMSE	0.838*	0.920*	0.827*	1											
5. Digit-span- forward	0.345*	0.492*	0.529*	0.480*	1										
6. Digit-span- backward	0.37*	0.497*	0.561*	0.521*	0.488*	1									
7. SVLT-immediate recall	0.617*	0.655*	0.718*	0.642*	0.340*	0.410*	1								
8. SVLT-delayed recall	0.620*	0.598*	0.686*	0.586*	0.219*	0.362*	0.780*	1							
9. SVLT-recognition	0.645*	0.594*	0.618*	0.572*	0.276*	0.297*	0.652*	0.703*	1						
10. RCFT-copy	0.492*	0.607*	0.602*	0.602*	0.350*	0.438*	0.463*	0.398*	0.315*	1					
11. SWF-animal	0.496*	0.550*	0.600*	0.549*	0.347*	0.374*	0.602*	0.565*	0.470*	0.453*	1				
12. SWF-supermarket items	0.537*	0.545*	0.624*	0.535*	0.255*	0.373*	0.610*	0.584*	0.495*	0.391*	0.655*	1			
13. PWF	0.373*	0.486*	0.575*	0.500*	0.471*	0.493*	0.452*	0.383*	0.370*	0.459*	0.579*	0.512*	1		
14. Stroop Color-Word (word reading)	0.377*	0.471*	0.423*	0.487*	0.284*	0.272*	0.243*	0.216*	0.224*	0.433*	0.311*	0.286*	0.336*	1	
15. Stroop Color-Word (color naming)	0.562*	0.610*	0.675*	0.625*	0.357*	0.444*	0.638*	0.594*	0.491*	0.452*	0.581*	0.591*	0.493*	0.282*	1
16. K-BNT	0.543*	0.617*	0.666*	0.643*	0.424*	0.416*	0.580*	0.531*	0.553*	0.515*	0.567*	0.478*	0.453*	0.346*	0.519*

Abbreviations: MMSE-2, Mini-Mental State Examination; BV, Brief version; SV, Standard version; EV, Expanded version; MMSE, Korean version of Mini-Mental State Examination; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; K-BNT, Korean version of Boston Naming Test.

Note.

* $p < 0.05$.

Table 15. Participants' average age, education, and gender classified by CDR & CDR-SOB stages (M±SD)

	N(91) CDR 0, CDR-SOB 0	MCI(226) CDR 0.5, CDR-SOB 0.5-2.5	EAD(35) CDR 0.5, CDR-SOB 3.0-4.0	MiAD(55) CDR 0.5, CDR-SOB 4.5-9.0	MoAD(7) CDR 0.5, CDR-SOB 9.5-15.5
Age	67.05±7.55	71.05±7.73*	76.00±6.33* [†]	75.60±7.98* [†]	70.57±9.78
Education	10.98±5.21	11.45±4.98	9.97±5.03	9.16±5.19 [†]	11.57±5.65
Male/Female	29/62	90/135	14/21	20/35	2/5

Abbreviations: CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; EAD, Early stage of Alzheimer' s Disease; MiAD, Mild stage of Alzheimer' s Disease; MoAD, Moderate stage of Alzheimer' s Disease.

Note.

* $p < 0.001$ for Normal vs. MCI, Normal vs. EAD, Normal vs. MiAD.

[†] $p < 0.01$ for MCI vs. EAD, MCI vs. MiAD.

[‡] $p < 0.05$ for MCI vs. MiAD.

Table 16. The results of the three versions of the MMSE-2 according to CDR & CDR-SOB (M±SD)

	N(1)	MCI(2)	EAD(3)	MiAD(4)	MoAD(5)			
MMSE-2	CDR 0, CDR-SOB 0	CDR 0.5, CDR-SOB 0.5-2.5	CDR 0.5, CDR-SOB 3.0-4.0	CDR 0.5, CDR-SOB 4.5-9.0	CDR 0.5, CDR-SOB 9.5-15.5	F	df	Post-hoc
BV	14.43±1.33	13.37±1.58	10.71±1.86	8.13±2.28	6.00±1.53	161.69*	4, 407	1>2>3>4>5
SV	27.26±2.66	25.71±2.35	22.03±2.85	18.35±3.5	14.43±3.60	151.66*	4, 407	1>2>3>4>5
EV	49.84±9.59	43.48±7.81	33.14±5.78	27.71±6.45	19.29±5.68	105.77*	4, 407	1>2>3>4=5

Abbreviations: M, Mean; SD, Standard deviation; MMSE-2; Mini-Mental State Examination; BV, Brief Version; SV, Standard Version; EV, Expanded Version; N, Normal; MCI, Mild Cognitive Impairment; EAD, Early stage of Alzheimer' s Disease; MiAD, Mild stage of Alzheimer' s Disease; MoAD, Moderate stage of Alzheimer' s Disease; 1, Normal; 2, Mild Cognitive Impairment; 3, Early stage of Alzheimer's Disease; 4, Mild stage of Alzheimer's Disease; 5, Moderate stage of Alzheimer's Disease.

Note.

* $p < 0.01$.

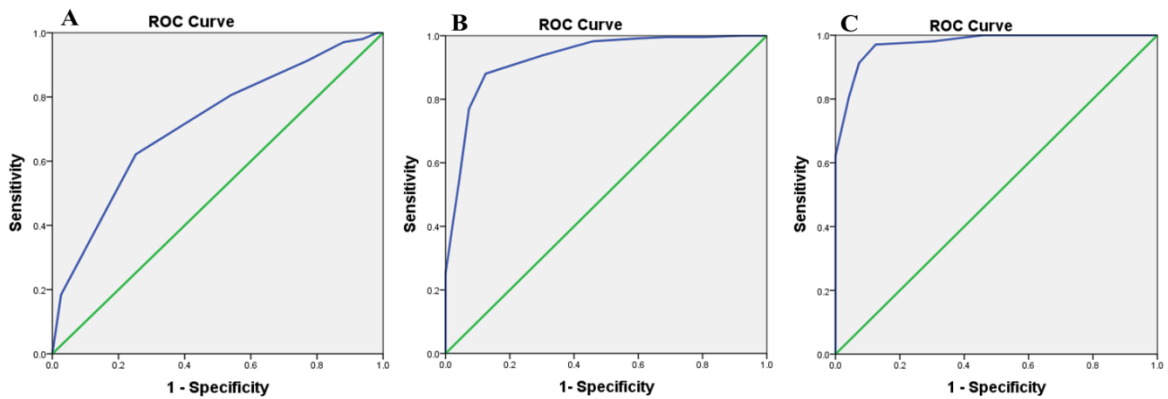


Figure 1. Mini-Mental State Examination-2: Brief Version (MMSE-2:BV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:BV in the groups of normal, mild cognitive impairment (MCI), and Alzheimer's Disease (AD). (A) Normal vs. MCI, Area Under the Curve (AUC) = 0.71. (B) MCI vs. AD, Area Under the Curve (AUC) = 0.93. (C) Normal vs. AD, Area Under the Curve (AUC) = 0.97.

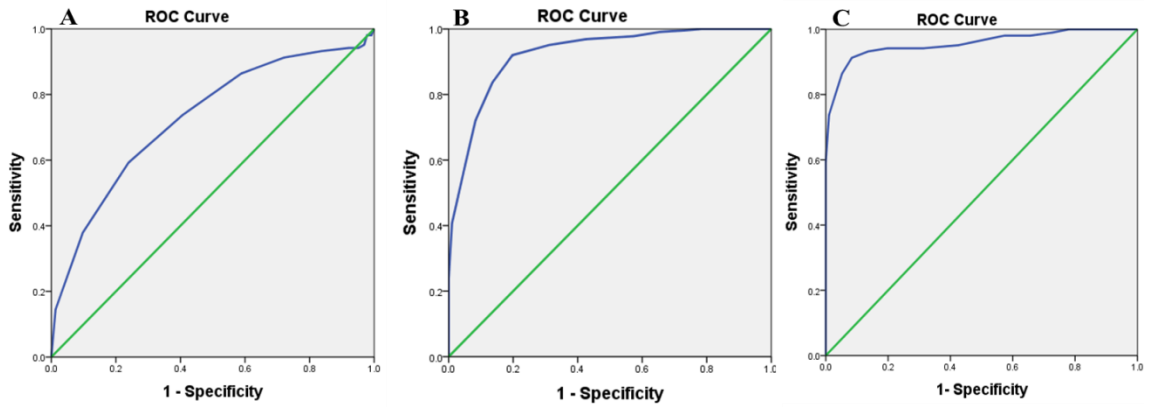


Figure 2. Mini-Mental State Examination-2:Standard Version (MMSE-2SV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:SV in the groups of normal, mild cognitive impairment (MCI), and Alzheimer's Disease (AD). (A) Normal vs. MCI, Area Under the Curve (AUC) = 0.72. (B) MCI vs. AD, Area Under the Curve (AUC) = 0.93. (C) Normal vs. AD, Area Under the Curve (AUC) = 0.95.

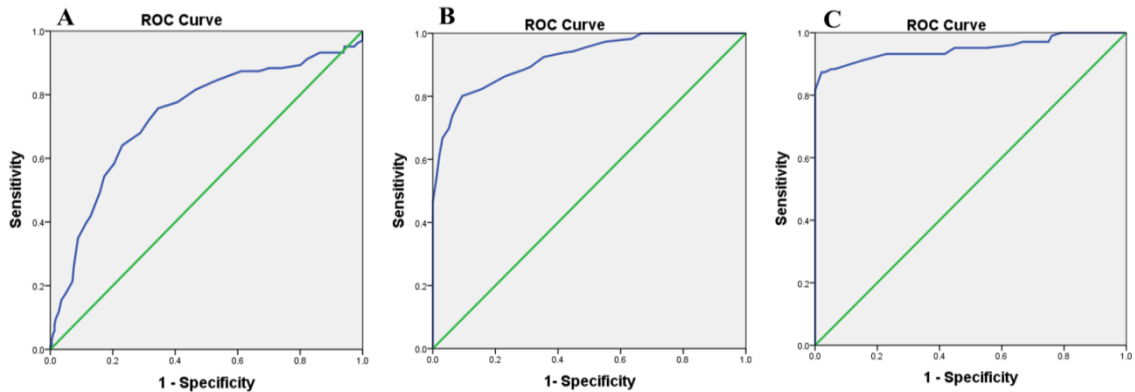


Figure 3. Mini-Mental State Examination-2:Expanded Version (MMSE-2:EV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:EV in the groups of normal, mild cognitive impairment (MCI), and Alzheimer's Disease (AD). (A) Normal vs. MCI, Area Under the Curve (AUC) = 0.73. (B) MCI vs. AD, Area Under the Curve (AUC) = 0.92. (C) Normal vs. AD, Area Under the Curve (AUC) = 0.94.

Study 2

Comparison between the Mini-Mental State Examination and the Mini-Mental State Examination-2 in Korean patients with Mild Cognitive Impairment and Alzheimer's Disease

Introduction

In study 1, the reliability and validity of the MMSE-2 in the patients with MCI, the patients with AD, and the healthy older adults were assessed in order to determine whether the MMSE-2 can be used clinically useful in Korea. The results were summarized as follows. There were significant differences in the MMSE-2 (BV, SV, and EV) across the patients with MCI, the patients with AD, and the healthy older adults. Moreover, the results of factor analysis showed that the MMSE-2 was varied according to the severity of cognitive impairment in each group, and it was confirmed that the items of the MMSE-2

were clearly divided for each group. The MMSE-2 and various neuropsychological assessments were highly correlated. Especially, the MMSE-2 was highly correlated with the K-MMSE, verbal memory test, and the frontal lobe function tests.

Moreover, the sensitivity and specificity of the three versions of the MMSE-2 (BV, SV, and EV) were relatively high in discriminating participants with normal cognitive aging from the patients with MCI and AD, so the MMSE-2 is a valid and reliable cognitive screening instrument for assessing cognitive impairment in Korean population, but its ability to distinguish the patients with MCI from those with normal cognitive aging may not be as highly sensitive as expected.

Therefore, in study 2, the purpose of this study is to compare the usefulness of the MMSE-2 (Folstein et al., 2010) and the K-MMSE (Kang et al., 1997) to determine which test is more sensitive in discriminating between normal cognitive aging and the patients with MCI or AD in a Korean population.

Materials and Methods

1. Participants

The groups of the patients (MCI and AD) and control participants were the same as study 1.

2. Instruments

2.1. MMSE-2

The description of the MMSE-2 was the same as that of study 1.

2.2. K-MMSE

The K-MMSE is a Korean version of the MMSE developed by Kang et al. (1997), and it is made in the same format as the original, and the total score of the K-MMSE is 30 points. In the K-MMSE, the items in the original MMSE (Folstein et al., 1975) are used as much as possible, but the orientation is separated by time and place. The overlapping pentagram for a 'Copy' test is included as an item of language test in the MMSE, but it is separated in the K-MMSE as a

'Visual construction.' In addition, although there are two items such as serial 7s and spelling the word "WORLD" backwards to evaluate 'Attention and calculation' in the MMSE, but serial 7s is only included in the K-MMSE. Therefore, the K-MMSE is composed of seven subtests in the following order: orientation to time (5 points), orientation to place (5 points), registration (3 points), attention and calculation (5 points), recall (3 points), language (8 points), and visual construction (1 point).

2.3. Other neuropsychological Assessments

The MMSE-2 and the K-MMSE were performed with a time interval of at least 1 hour in order to compensate for the learning effect that could be occurred when using the MMSE-2 and the K-MMSE at the same time, and the detailed neuropsychological assessments were performed in the meantime. In the detailed neuropsychological assessments, there were Seoul Verbal Learning Test (SVLT) (Kang et al., 2003) for assessing verbal memory, a copy of the Rey Complex Figure

Test for assessing visuospatial function (Meyers et al., 1995), the Semantic Word Fluency Test (SWT) and the Phonemic Word Fluency Test (PWF) (Kang et al., 2000) and the Korean-Color Word Stroop Test (K-CWST) (Lee et al., 2000) for assessing executive function of the frontal lobe, the Korean version of the Boston Naming Test (K-BNT) (Kim et al., 1997) for assessing naming ability, and forward and backward digit span test for assessing attention. Moreover, global measurements, including CDR (Morris, 1993) & CDR-SOB (O'Bryant et al., 2008, 2010), were also conducted.

3. Procedure

There were overlapping subtests in the MMSE-2 and the K-MMSE (eg: orientation to time, orientation to place, attention and calculation, writing, and drawing). The overlapping subtests were not repeated and scored equally. However, in the case of the attention and calculation test, it was repeated because the three words should be learned and recalled between this test, but the score was given to the same as the score of the test which was conducted at first. Even if the items were

the same, if the content of the test was different from one test to another, questions were taken and scored separately. The order of the detailed neuropsychological assessments including the MMSE-2 and the K-MMSE was the same as in study 1.

4. Statistical analysis

First, an analysis of variance (ANOVA) was used to compare age and education levels, and a chi square test was used to compare gender across the three groups (226 patients with MCI, 97 patients with AD, and 91 healthy older adults).

Second, the results of the MMSE-2 (BV, SV, and EV) in the three groups were analyzed using an analysis of covariance (ANCOVA) after controlling for demographic variables (age and education).

Third, the results of the K-MMSE in the three groups were analyzed using an ANCOVA after controlling for demographic variables (age and education).

Fourth, the discriminant analysis was performed to examine the classification accuracy and discrimination of the patients with MCI and AD in the MMSE-2 and the K-MMSE.

Finally, to evaluate the sensitivity and specificity of the MMSE-2 and the K-MMSE for differentiating among the three groups were examined using a receiver operating characteristic (ROC) curve and area under the curve (AUC) measurements.

Data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be significant for all analyses.

Results

1. The participants' demographic data

The demographic characteristics of the patients with MCI, the patients with AD, and the healthy older adults were the same as those of study 1.

2. The results of participants' neuropsychological assessments

The results of the neuropsychological assessments in the three groups were the same as those of study 1.

3. The results of the MMSE-2 in the groups of normal, MCI, and AD

3.1. MMSE-2:BV, SV, EV

The results of the MMSE-2 (BV, SV, and EV) in the three groups were the same as those of study 1.

4. The results of the K-MMSE in the groups of normal, MCI, and AD

The results of the K-MMSE scores in the three groups are presented in Table 1. An ANCOVA that controlled for age and education revealed significant differences among the three groups on the K-MMSE. According to Tukey's *post hoc* analyses, the scores of recall and total in the K-MMSE were significantly higher for the healthy older adults than for the group of patients (MCI and AD), and they were significantly higher for the patients with MCI than for the patients with AD. However, there were no significant differences in the subtests such as registration, orientation to time, orientation to place, attention and calculation, language, and drawing between the healthy older adults and the patients with MCI, but the scores of six subtests in the K-MMSE were significantly higher for the healthy older adults and the patients with MCI than for the patients with AD.

5. Comparison of the discriminant analysis between the MMSE-2 and the K-MMSE

5.1. MMSE-2

5.1.1. The discriminant analysis of the MMSE-2 in the groups of normal, MCI, and AD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the three groups (healthy older adults, MCI, and AD) as dependent variables. Two significant discriminant functions were calculated through analysis, and the results are shown in Table 2. The results showed that the first function distinguished between the healthy older adults vs. the group of patients (MCI and AD), and the second function distinguished between the patient with MCI vs. the patients with AD. The first function was statistically significant, explained 92.1% of the total variance in the model (Wilk's Lambda = 0.342, $\chi^2 = 436.80$, $p < 0.001$), and the second function was also statistically significant,

explained 7.9% of the total variance in the model (Wilk's Lambda = 0.881, $\chi^2 = 51.51$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest in the first function (Normal vs. MCI and AD), and story memory was the most discriminating subtest in the second function (MCI vs. AD) (Table 3). The structure matrix canonical loadings of the predictor variables and the two discriminant functions indicated that the first function was strongly correlated with orientation to time (canonical loading = 0.78), orientation to place (canonical loading = 0.58), recall (canonical loading = 0.55), processing speed (canonical loading = 0.42), and attention and calculation (canonical loading = 0.33). The second function was strongly correlated with story memory (canonical loading = -0.66) (Table 4). These results indicated that the best discriminating subtest between the healthy older adults and the group of patients (MCI and AD) was orientation to time, and the best discriminating subtest between the patients with MCI and the patients with AD was story memory.

The results of classifying the samples by the two functions are presented in Table 5. According to the classification results, in the MMSE-2:BV, 55.3% of the patients with MCI, 78.4% of the patients with AD, and 72.5% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 64.5%. In the MMSE-2:SV, 58.0% of the patients with MCI, 79.4% of the patients with AD, and 72.5% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 66.2%. In the MMSE-2:EV, 68.6% of the patients with MCI, 78.4% of the patients with AD, and 72.5% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 71.7%.

5.1.2. The discriminant analysis of the MMSE-2 in the healthy older adults vs. the patients with MCI

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the two groups (healthy older adults and MCI) as

dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 6. There was significant difference between the two groups over nine independent variables (Wilk's Lambda = 0.790, $\chi^2 = 73.35$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, story memory was the most discriminating subtest (Table 7). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with story memory (canonical loading = 0.88), recall (canonical loading = 0.70), processing speed (canonical loading = 0.38), and orientation to time (canonical loading = 0.34), but the function was not significantly correlated with attention and calculation, orientation to place, drawing, language, and registration (Table 8). These results indicated that the best discriminating subtest between the healthy older adults and the patients with MCI was story memory.

The results of classifying the samples by the function are presented in Table 9. According to the classification results, in the MMSE-2:BV,

73.6% of the healthy older adults and 64.2% of the patients with MCI were correctly classified, and thus the overall classification accuracy was 66.9%. In the MMSE-2:SV, 71.4% of the healthy older adults and 65.0% of the patients with MCI were correctly classified, and thus the overall classification accuracy was 66.9%. In the MMSE-2:EV, 73.6% of the healthy older adults and 74.8% of the patients with MCI were correctly classified, and thus the overall classification accuracy was 74.4%.

5.1.3. The discriminant analysis of the MMSE-2 in the patients with MCI vs. the patients with AD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the two groups (MCI and AD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 10. There was significant difference

between the two groups over nine independent variables (Wilk's Lambda = 0.129, $\chi^2 = 268.22$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest (Table 11). In addition, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with orientation to time (canonical loading = 0.81), orientation to place (canonical loading = 0.61), story memory (canonical loading = 0.53), recall (canonical loading = 0.49), processing speed (canonical loading = 0.43), and attention and calculation (canonical loading = 0.35), but the function was not significantly correlated with registration, language, and drawing (Table 12). These results indicated that the best discriminating subtest between the patients with MCI and the patients with AD was orientation to time.

The results of classifying the samples by the function are presented in Table 13. According to the classification results, in the MMSE-2:BV, 89.4% of the patients with MCI and 81.4% of the patients with AD

were correctly classified, and thus the overall classification accuracy was 87.0%. In the MMSE-2:SV, 92.5% of the patients with MCI and 82.5% of the patients with AD were correctly classified, and thus the overall classification accuracy was 89.5%. In the MMSE-2:EV, 92.0% of the patients with MCI and 82.5% of the patients with AD were correctly classified, and thus the overall classification accuracy was 89.2%.

5.1.4. The discriminant analysis of the MMSE-2 in the healthy older adults vs. the patients with AD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the two groups (healthy older adults and AD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 14. There was significant difference between the two groups over nine independent variables (Wilk's Lambda = 0.247, $\chi^2 = 253.62$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, story memory was the most discriminating subtest (Table 15). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with story memory (canonical loading = 0.75), recall (canonical loading = 0.67), orientation to time (canonical loading = 0.61), orientation to place (canonical loading = 0.44), processing speed (canonical loading = 0.44), and attention and calculation (canonical loading = 0.31), but the function was not significantly correlated with drawing, registration, and language (Table 16). These results indicated that the best discriminating subtest between the healthy older adults and the patients with AD was story memory.

The results of classifying the samples by the function are presented in Table 17. According to the classification results, in the MMSE-2:BV, 91.2% of the healthy older adults and 88.7% of the patients with AD were correctly classified, and thus the overall classification accuracy was 89.9%. In the MMSE-2:SV, 91.2% of the healthy older adults and

89.7% of the patients with AD were correctly classified, and thus the overall classification accuracy was 90.4%. In the MMSE-2:EV, 93.4% of the healthy older adults and 97.9% of the patients with AD were correctly classified, and thus the overall classification accuracy was 95.7%.

5.2. K-MMSE

5.2.1. The discriminant analysis of the K-MMSE in the groups of normal, MCI, and AD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the three groups (healthy older adults, MCI, and AD) as dependent variables. Two significant discriminant functions were calculated through analysis, and the results are shown in Table 18. The results showed that the first function distinguished between the healthy older adults and the group of patients (MCI and AD), and the second function distinguished between the patients with MCI and the patients

with AD. The first function was statistically significant, explained 97.4% of the total variance in the model (Wilk's Lambda = 0.395, $\chi^2 = 397.15$, $p < 0.001$), and the second function was also statistically significant, explained 2.6% of the total variance in the model (Wilk's Lambda = 0.963, $\chi^2 = 15.28$, $p < 0.05$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest in the first function, and recall was the most discriminating subtest in the second function (Table 19).

The structure matrix canonical loadings of the predictor variables and the two discriminant functions indicated that the first function was strongly correlated with orientation to time (canonical loading = 0.83), orientation to place (canonical loading = 0.61), language (canonical loading = 0.42), and attention and calculation (canonical loading = 0.35). The second function was very strongly correlated with recall (canonical loading = 0.84) (Table 20). These results indicated that the best discriminating subtest between the healthy older adults and the group

of patients was orientation to time, and the best discriminating subtest between the patients with MCI and the patients with AD was recall.

The results of classifying the samples by the two functions are presented in Table 21. According to the classification results, 83.6% of the patients with MCI, 68.0% of the patients with AD, and 28.6% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 67.9%.

5.2.2. The discriminant analysis of the K-MMSE in the healthy older adults vs. the patients with MCI

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (healthy older adults and MCI) as dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 22. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.905, $\chi^2 = 30.96$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, recall was the most discriminating subtest (Table 23). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with recall (canonical loading = 0.81), orientation to time (canonical loading = 0.55), language (canonical loading = 0.43), attention and calculation (canonical loading = 0.37), and orientation to place (canonical loading = 0.36), but the function was not significantly correlated with registration and drawing (Table 24). These results indicated that the best discriminating subtest between the healthy older adults and the patients with MCI was recall.

The results of classifying the samples by the function are presented in Table 25. According to the classification results, 69.2% of the healthy older adults and 61.1% of the patients with MCI were correctly classified, and thus the overall classification accuracy was 63.4%.

5.2.3. The discriminant analysis of the K-MMSE in the patients with MCI vs. the patients with AD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (MCI and AD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 26. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.443, $\chi^2 = 258.82$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest (Table 27). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with orientation to time (canonical loading = 0.83), orientation to place (canonical loading = 0.63), recall (canonical loading = 0.43), language (canonical loading = 0.40), and attention and calculation (canonical loading = 0.36), but the function was not significantly correlated with

drawing and registration (Table 28). These results indicated that the best discriminating subtest between the patients with MCI and the patients with AD was orientation to time.

The results of classifying the samples by the function are presented in Table 29. According to the classification results, 92.0% of the patients with MCI and 81.4% of the patients with AD were correctly classified, and thus the overall classification accuracy was 88.9%.

5.2.4. The discriminant analysis of the K-MMSE in the healthy older adults vs. the patients with AD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (healthy older adults and AD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are shown in Table 30. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.294, $\chi^2 = 223.55$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, recall was the most discriminating subtest (Table 31). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with orientation to time (canonical loading = 0.69), recall (canonical loading = 0.65), orientation to place (canonical loading = 0.50), language (canonical loading = 0.36), and attention and calculation (canonical loading = 0.35), but the function was not significantly correlated with drawing and registration (Table 32). These results indicated that the best discriminating subtest between the healthy older adults and the patients with AD was orientation to time.

The results of classifying the samples by the function are presented in Table 33. According to the classification results, 95.6% of the healthy older adults and 94.8% of the patients with AD were correctly classified, and thus the overall classification accuracy was 95.2%.

6. Diagnostic utility of the MMSE-2 and the K-MMSE

6.1. MMSE-2

The results of each version of the MMSE-2 (BV, SV, and EV) were the same as in study 1.

6.2. K-MMSE

The ROC curve analysis and the area under the curve (AUC) was performed to verify the diagnostic utility of the K-MMSE in the three groups (MCI, AD, and healthy older adults).

First, for discriminating the healthy older adults from the patients with MCI, the AUC of the K-MMSE was 0.70 (95% confidence interval, CI, 0.64-0.77, $p < 0.001$). The sensitivity of the K-MMSE was 70% and the specificity was 59% when using a cut-off score of ≤ 26 of 30 to predict MCI. Second, for discriminating the patients with MCI from the patients with AD, the AUC of the K-MMSE was 0.94 (95% CI, 0.91-0.96, $p < 0.001$). The sensitivity of the K-MMSE was 84% and the specificity was 88% when using a cut-off score ≤ 23 of 30 to predict AD. Finally, for discriminating the healthy older adults from the patients with AD,

the AUC of the K-MMSE was 0.97 (95% CI, 0.95–0.99, $p < 0.001$). The sensitivity of the K-MMSE was 95% and the specificity was 78% when using a cut-off score ≤ 22 of 30 to predict AD (Figure 1).

7. Comparison between the MMSE-2 and the K-MMSE

7.1. Comparison between the healthy older adults and the patients with MCI

7.1.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults vs. the patients with MCI. The AUC of the MMSE-2:BV was 0.708, and the AUC of the K-MMSE was 0.703, but there was no significant difference between the two tests (Table 34).

7.1.2. The MMSE-2:SV vs. the K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults vs. the patients with MCI. The AUC of the MMSE-2:SV was 0.720, and the AUC of the K-MMSE was 0.703, but there was no significant difference between the two tests (Table 34).

7.1.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults vs. the patients with MCI. The AUC of the MMSE-2:EV was 0.728, and the AUC of the K-MMSE was 0.703, but there was no significant difference between the two tests (Table 34).

7.2. Comparison between the patients with MCI and the patients with AD

7.2.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the patients with MCI vs. the patients with AD. The AUC of the MMSE-2:BV was 0.903, and the AUC of the K-MMSE was 0.936, but there was no significant difference between the two tests (Table 35).

7.2.2. The MMSE-2:SV vs. the K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the patients with MCI vs. the patients with AD. The AUC of the MMSE-2:SV was 0.925, and the AUC of the K-MMSE was 0.936, but there was no significant difference between the two tests (Table 35).

7.2.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in

discriminating between the patients with MCI vs. the patients with AD. The AUC of the MMSE-2:EV was 0.921, and the AUC of the K-MMSE was 0.936, but there was no significant difference between the two tests (Table 35).

7.3. Comparison between the healthy older adults and the patients with AD

7.3.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults vs. the patients with AD. The AUC of the MMSE-2:BV was 0.973, and the AUC of the K-MMSE was 0.971, but there was no significant difference between the two tests (Table 36).

7.3.2. The MMSE-2:SV vs. the K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in

discriminating between the healthy older adults vs. the patients with AD. The AUC of the MMSE-2:SV was 0.952, and the AUC of the K-MMSE was 0.971, but there was no significant difference between the two tests (Table 36).

7.3.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults vs. the patients with AD. The AUC of the MMSE-2:EV was 0.943, and the AUC of the K-MMSE was 0.971, but there was no significant difference between the two tests (Table 36).

Discussion

In study 2, the cognitive screening tests, the MMSE-2 and the K-MMSE, were compared to determine which test was more sensitive in discriminating across the three groups (healthy older adults, MCI, and AD). The results demonstrated several key points.

First, the results of the MMSE-2 (BV, SV, and EV) and the K-MMSE were significantly differed across the three groups (healthy older adults, MCI, and AD). In all three versions of the MMSE-2, the subtests in the MMSE-2 such as recall, story memory, and processing speed of the healthy older adults were significantly higher than those of the patients with MCI and AD, and also the items in the MMSE-2 of the patients with MCI were significantly higher than those of the patients with AD. Therefore, deficits in verbal memory were most pronounced.

In addition, in the K-MMSE, the subtest in the K-MMSE such as recall of the healthy older adults were significantly higher than those of the patients with MCI and AD, and also the item in the K-MMSE for the patients with MCI was significantly higher than those of the patients with AD.

When comparing the magnitude of the recall test in the MMSE-2 ($\eta^2 = 0.27$) and the K-MMSE ($\eta^2 = 0.19$), the recall test in the MMSE-2 could be seen to discriminate each group slightly more sensitively than the K-MMSE. Moreover, among the verbal memory tests, when comparing the magnitude of the story memory test in the MMSE-2 ($\eta^2 = 0.35$) with the recall tests in the MMSE-2 ($\eta^2 = 0.27$) and the K-MMSE ($\eta^2 = 0.19$), the story memory was the most sensitive among verbal memory tests to distinguish in each group. Thus, verbal memory tests (recall and story memory) included in the MMSE-2 might be more sensitive to differentiate across the three groups (healthy older adults, MCI and AD).

Second, the results of the discriminant analysis of the MMSE-2 were as follows. In the MMSE-2, the subtests that discriminated significantly between the healthy older adults and the groups of patients (MCI and AD) were orientation to time, orientation to place, recall, processing speed, and attention and calculation. Moreover, the subtest which discriminated significantly between the patients with MCI and the patients with AD was story memory. The subtests such as orientation

to time, orientation to place, recall, and story memory in the MMSE-2 are all tests which measure episodic memory, and the subtests such as processing speed and attention and calculation are the tests that measure psychomotor ability and working memory of the frontal lobe. As shown in many previous studies, these results suggested that measuring episodic memory is an important variable in group discrimination because episodic memory is one of the first deteriorating functions in patients with MCI or AD (Backman et al., 2005; Bennett et al., 2002; Chen et al., 2000; Grober et al., 2008).

In addition, in the MMSE-2, the subtests that discriminated significantly between the healthy older adults and the patients with MCI were story memory, recall, processing speed, and orientation to time. These results also showed that the tests related with episodic memory are the most sensitive tests for group discrimination, which is a result of supporting previous studies (Backman et al., 2005; Bennett et al., 2002; Chen et al., 2000; Grober et al., 2008). The subtests that discriminated significantly between the patients with MCI and the patients with AD in the MMSE-2 were orientation to time, orientation

to place, story memory, recall, processing speed, and attention and calculation, and these results showed that as the dementia progresses, not only episodic memory but also the frontal lobe function has been decreased.

Third, the results of the discriminant analysis of the K-MMSE were as follows. In the K-MMSE, the subtests that discriminated significantly across the three groups (healthy older adults, MCI, and AD) were orientation to time, orientation to place, language, and attention and calculation. Moreover, the subtest in the K-MMSE that discriminated significantly between the patients with MCI and the patients with AD was recall. In the K-MMSE, as in the MMSE-2, these results also showed that measuring episodic memory is most sensitive for group discrimination.

In addition, in the K-MMSE, the subtests that discriminated significantly between the healthy older adults and the patients with MCI were recall, orientation to time, language, and attention and calculation. These tests are the most sensitive measures for episodic memory and working memory. The subtests that distinguished significantly between

the patients with MCI and the patients with AD were orientation to time, orientation to place, recall, language, and attention and calculation, and these results also showed that as the dementia progresses, not only episodic memory but also frontal lobe function has been decreased. In conclusion, the tests related with episodic memory are the most sensitive tests for group discrimination in both the MMSE-2 and the K-MMSE.

Comparing the results of the discriminant analysis of the MMSE-2 and the K-MMSE comprehensively, the classification accuracy of the MMSE-2 in the three groups was 71.7%, and the classification accuracy of the K-MMSE in the three groups was 67.9%, suggesting that the MMSE-2 was more accurate than the K-MMSE. In more detail, the accuracy rate of classifying the healthy older adults and the patients with MCI was 74.4% for the MMSE-2 and 63.4% for the K-MMSE, suggesting that the MMSE-2 was more sensitive and accurate than the K-MMSE. Moreover, the accuracy of classification of the patients with MCI and the patients with AD was 89.2% for the MMSE-2 and 88.9% for the K-MMSE, suggesting that the accuracy of classification of both

tests was similar. Finally, the accuracy of classification of the healthy older adults and the patients with AD was 95.7% for the MMSE-2 and 95.2% for the K-MMSE, suggesting that these two tests were similar.

In summary, the MMSE-2 was a more sensitive test than the K-MMSE when discriminating across the three groups. Especially, the MMSE-2 is about 10% more accurate than the K-MMSE when discriminating between the healthy older adults and the patients with MCI. However, there was no significant difference between the two tests when discriminating between the healthy older adults and the patients with AD or between the patients with MCI and the patients with AD.

Finally, when the AUC of the MMSE-2 and the K-MMSE were compared, there was no significant difference between the two tests in all tests. However, the MMSE-2:SV and the MMSE-2:EV might be slightly more sensitive than the K-MMSE in distinguishing between the healthy older and the patients with MCI, and rather the MMSE-2:BV and the K-MMSE might be seem to discriminate slightly more sensitive when discriminating the patients with AD from the healthy older adults

and the patients with MCI. In other words, when discriminating between the healthy older adults and the patients with MCI, the more difficult test was better for group discrimination, and when discriminating the patients with AD from the healthy older adults and the patients with MCI, it was shown that the test with easy difficulty was better for group discrimination.

The overall results showed that as for the development purpose of the MMSE-2, when discriminating between the healthy older adults and the group of patients (MCI and AD), the MMSE-2:SV and MMSE-2:EV are more sensitive and accurate to detect early cognitive decline than the K-MMSE or the MMSE-2:BV, but as the dementia progresses, the K-MMSE or the MMSE-2:BV may be more useful for group discrimination than the MMSE-2:SV and the MMSE-2:EV. Thus, the MMSE-2 appears to be more useful as a cognitive screening test in clinical settings than the K-MMSE.

Table 1. The results of the K-MMSE in the groups of normal, MCI, and AD (M \pm SD)

K-MMSE	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Orientation to time	4.80 \pm 0.43	4.54 \pm 0.77	2.40 \pm 1.52	175.53*	2, 409	0.46	1=2>3
Orientation to place	4.86 \pm 0.38	4.73 \pm 0.53	3.62 \pm 1.06	91.73*	2, 409	0.31	1=2>3
Registration	3.00 \pm 0.00	2.98 \pm 0.13	2.94 \pm 0.24	3.13 [†]	2, 409	0.02	1=2>3
Attention and Calculation	4.09 \pm 1.17	3.77 \pm 1.24	2.61 \pm 1.56	28.29*	2, 409	0.12	1=2>3
Recall	1.74 \pm 1.07	1.12 \pm 1.07	0.15 \pm 0.36	48.01*	2, 409	0.19	1>2>3
Language	7.88 \pm 0.36	7.71 \pm 0.61	6.90 \pm 1.18	40.06*	2, 409	0.16	1=2>3
Drawing	0.95 \pm 0.23	0.90 \pm 0.30	0.69 \pm 0.47	13.54*	2, 409	0.06	1=2>3
Total	27.31 \pm 2.30	25.75 \pm 2.46	19.31 \pm 3.80	229.27 [†]	2, 409	0.53	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; K-MMSE, Korean version of the Mini-Mental State Examination; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.001$.

[†] $p < 0.01$.

[‡] $p < 0.05$.

Table 2. The results by the discriminant functions analysis in the groups of normal, MCI, and AD (MMSE-2)

Functions	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	1.577	92.1	92.1	0.782	0.342	436.801	18	0.000
2	0.135	7.9	100.0	0.345	0.881	51.510	8	0.000

Abbreviation: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 3. The standardized canonical discriminant function coefficients in the groups of normal, MCI, and AD (MMSE-2)

	Functions	
	1	2
Registration	0.014	0.189
Orientation to time	0.573	0.469
Orientation to place	0.292	0.253
Recall	0.265	-0.298
Attention and calculation	0.072	0.161
Language	-0.047	0.178
Drawing	0.100	0.032
Story memory	0.346	-0.754
Processing speed	-0.033	-0.085

Abbreviation: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 4. The results of the structure matrix in the groups of normal, MCI, and AD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions	
	Function 1	Function 2
Orientation to time	0.784*	0.422
Orientation to place	0.578*	0.330
Recall	0.547*	-0.449
Processing speed	0.420*	-0.107
Attention and calculation	0.334*	0.041
Registration	0.234*	0.207
Language	0.231*	0.074
Drawing	0.210*	0.162
Story memory	0.608	-0.661*

Abbreviation: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 5. Classification rates (%) by discriminant analysis in the groups of normal, MCI, and AD (MMSE-2)

MMSE-2		Predictive groups				
		Groups	Normal	MCI	AD	Total
BV	Frequency	Normal	66	24	1	91
		MCI	82	125	19	226
		AD	0	21	76	97
	%	Normal	72.5	26.4	1.1	100.0
		MCI	36.3	55.3	8.4	100.0
		AD	0.0	21.6	78.4	100.0
MMSE-2:BV Classification accuracy						64.5%
SV	Frequency	Normal	66	23	2	91
		MCI	79	131	16	226
		AD	0	20	77	97
	%	Normal	72.5	25.3	2.2	100.0
		MCI	35.0	58.0	7.1	100.0
		AD	0.0	20.6	79.4	100.0
MMSE-2:SV Classification accuracy						66.2%
EV	Frequency	Normal	66	23	2	91
		MCI	54	155	17	226
		AD	0	21	76	97
	%	Normal	72.5	25.3	2.2	100.0
		MCI	23.9	68.6	7.5	100.0
		AD	0.0	21.6	78.4	100.0
MMSE-2:EV Classification accuracy						71.7%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Table 6. The result by the discriminant function analysis in the healthy older adults and the patients with MCI (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	0.266	100.0	100.0	0.459	0.790	73.352	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 7. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with MCI (MMSE-2)

	Function 1
Registration	-0.176
Orientation to time	0.117
Orientation to place	0.008
Recall	0.366
Attention and calculation	-0.080
Language	-0.199
Drawing	0.016
Story memory	0.813
Processing speed	0.026

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 8. The results of the structure matrix in the healthy older adults and the patients with MCI (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Story memory	0.883
Recall	0.697
Processing speed	0.378
Orientation to time	0.341
Attention and calculation	0.230
Orientation to place	0.228
Drawing	0.133
Language	0.031
Registration	0.012

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 9. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with MCI (MMSE-2)

MMSE-2		Predictive groups			
		Groups	Normal	MCI	Total
BV	Frequency	Normal	67	24	91
		MCI	81	145	226
	%	Normal	73.6	26.4	100.0
		MCI	35.8	64.2	100.0
	MMSE-2:BV Classification accuracy				66.9%
		Predictive groups			
		Groups	Normal	MCI	Total
SV	Frequency	Normal	65	26	91
		MCI	79	147	226
	%	Normal	71.4	28.6	100.0
		MCI	35.0	65.0	100.0
	MMSE-2:SV Classification accuracy				66.9%
		Predictive groups			
		Groups	Normal	MCI	Total
EV	Frequency	Normal	67	24	91
		MCI	57	169	226
	%	Normal	73.6	26.4	100.0
		MCI	25.2	74.8	100.0
	MMSE-2:EV Classification accuracy				74.4%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; MCI, Mild Cognitive Impairment.

Table 10. The result by the discriminant function analysis in the patients with MCI and the patients with AD (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	1.334	100.0	100.0	0.756	0.129	268.222	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 11. The standardized canonical discriminant function coefficients in the patients with MCI and the patients with AD (MMSE-2)

	Function 1
Registration	0.087
Orientation to time	0.585
Orientation to place	0.311
Recall	0.238
Attention and calculation	0.139
Language	-0.024
Drawing	0.093
Story memory	0.257
Processing speed	-0.011

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 12. The results of the structure matrix in the patients with MCI and the patients with AD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Orientation to time	0.809
Orientation to place	0.609
Story memory	0.530
Recall	0.494
Processing speed	0.426
Attention and calculation	0.345
Registration	0.284
Language	0.265
Drawing	0.237

Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 13. Classification rates (%) by discriminant analysis in the patients with MCI and the patients with AD (MMSE-2)

MMSE-2		Predictive groups			
		Groups	MCI	AD	Total
BV	Frequency	MCI	202	24	226
		AD	18	79	97
	%	MCI	89.4	10.6	100.0
		AD	18.6	81.4	100.0
MMSE-2:BV Classification accuracy					87.0%
		Predictive groups			
		Groups	MCI	AD	Total
SV	Frequency	MCI	209	17	226
		AD	17	80	97
	%	MCI	92.5	7.5	100.0
		AD	17.5	82.5	100.0
MMSE-2:SV Classification accuracy					89.5%
		Predictive groups			
		Groups	MCI	AD	Total
EV	Frequency	MCI	208	18	226
		AD	17	80	97
	%	MCI	92.0	8.0	100.0
		AD	17.5	82.5	100.0
MMSE-2:EV Classification accuracy					89.2%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Table 14. The result by the discriminant function analysis in the healthy older adults and the patients with AD (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	3.044	100.0	100.0	0.868	0.247	253.615	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 15. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with AD (MMSE-2)

	Function
	1
Registration	-0.060
Orientation to time	0.423
Orientation to place	0.224
Recall	0.389
Attention and calculation	-0.074
Language	-0.078
Drawing	0.170
Story memory	0.553
Processing speed	-0.045

Abbreviations: MMSE-2, Mini-Mental State Examination-2; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 16. The results of the structure matrix in the healthy older adults and the patients with AD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Story memory	0.745
Recall	0.670
Orientation to time	0.611
Orientation to place	0.444
Processing speed	0.438
Attention and calculation	0.308
Drawing	0.198
Registration	0.173
Language	0.152

Abbreviations: MMSE-2, Mini-Mental State Examination-2; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 17. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with AD (MMSE-2)

MMSE-2		Predictive groups			
		Groups	Normal	AD	Total
BV	Frequency	Normal	83	8	91
		AD	11	86	97
	%	Normal	91.2	8.8	100.0
		AD	11.3	88.7	100.0
	MMSE-2:BV Classification accuracy				89.9%
		Predictive groups			
		Groups	Normal	AD	Total
SV	Frequency	Normal	83	8	91
		AD	10	87	97
	%	Normal	91.2	8.8	100.0
		AD	10.3	89.7	100.0
	MMSE-2:SV Classification accuracy				90.4%
		Predictive groups			
		Groups	Normal	AD	Total
EV	Frequency	Normal	85	6	91
		AD	2	95	97
	%	Normal	93.4	6.6	100.0
		AD	2.1	97.9	100.0
	MMSE-2:EV Classification accuracy				95.7%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; AD, Alzheimer's Disease.

Table 18. The result by the discriminant functions analysis in the groups of normal, MCI, and AD (K-MMSE)

Functions	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	1.440	97.4	97.4	0.768	0.395	379.151	14	0.000
2	0.038	2.6	100.0	0.192	0.963	15.281	6	0.018

Abbreviation: K-MMSE, Korean version of the Mini-Mental State Examination; Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 19. The standardized canonical discriminant function coefficients in the groups of normal, MCI, and AD (K-MMSE)

	Functions	
	1	2
Orientation to time	0.651	-0.357
Orientation to place	0.285	-0.323
Registration	-0.033	0.182
Attention and calculation	0.131	0.129
Recall	0.331	0.905
Language	0.183	0.060
Drawing	0.075	-0.043

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 20. The results of the structure matrix in the groups of normal, MCI, and AD (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions	
	Function 1	Function 2
Orientation to time	0.829*	-0.328
Orientation to place	0.612*	-0.277
Language	0.415*	0.018
Attention and calculation	0.349*	0.121
Drawing	0.243*	-0.002
Registration	0.119*	0.109
Recall	0.455	0.837*

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, Normal vs. MCI & AD; 2, MCI vs. AD.

Table 21. Classification rates (%) by discriminant analysis in the groups of normal, MCI, and AD (K-MMSE)

		Predictive groups			
	Groups	Normal	MCI	AD	Total
Frequency	Normal	26	64	1	91
	MCI	25	189	12	226
	AD	0	31	66	97
%	Normal	28.6	70.3	1.1	100.0
	MCI	11.1	83.6	5.3	100.0
	AD	0.0	32.0	68.0	100.0
Classification accuracy					67.9%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Table 22. The result by the discriminant function analysis in the healthy older adults and the patients with MCI (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	0.105	100	100	0.308	0.905	30.961	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 23. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with MCI (K-MMSE)

	Function
	1
Orientation to time	0.343
Orientation to place	0.064
Registration	0.121
Attention and calculation	0.233
Recall	0.703
Language	0.262
Drawing	-0.017

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 24. The results of the structure matrix in the healthy older adults and the patients with MCI (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Recall	0.808
Orientation to time	0.545
Language	0.434
Attention and calculation	0.367
Orientation to place	0.364
Registration	0.222
Drawing	0.213

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; 1, Normal vs. MCI.

Table 25. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with MCI (K-MMSE)

		Predictive groups		
	Groups	Normal	MCI	Total
Frequency	Normal	63	28	91
	MCI	88	138	226
%	Normal	69.2	30.8	100.0
	MCI	38.9	61.1	100.0
Classification accuracy				63.4%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment.

Table 26. The result by the discriminant function analysis in the patients with MCI and the patients with AD (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk' s Lambda	Chi-Square	df	p
1	1.260	100.0	100.0	0.747	0.443	258.822	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 27. The standardized canonical discriminant function coefficients in the patients with MCI and the patients with AD (K-MMSE)

	Function
	1
Orientation to time	0.650
Orientation to place	0.303
Registration	-0.057
Attention and calculation	0.174
Recall	0.292
Language	0.173
Drawing	0.072

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 28. The results of the structure matrix in the patients with MCI and the patients with AD (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Orientation to time	0.833
Orientation to place	0.627
Recall	0.431
Language	0.404
Attention and calculation	0.355
Drawing	0.244
Registration	0.105

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; 1, MCI vs. AD.

Table 29. Classification rates (%) by discriminant analysis in the patients with MCI and the patients with AD (K-MMSE)

		Predictive groups		
	Groups	MCI	AD	Total
Frequency	MCI	208	18	226
	AD	18	79	97
%	MCI	92.0	8.0	100.0
	AD	18.6	81.4	100.0
Classification accuracy				88.9%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Table 30. The result by the discriminant function analysis in the healthy older adults and the patients with AD (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	2.404	100.0	100.0	0.840	0.294	223.545	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 31. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with AD (K-MMSE)

	Function
	1
Orientation to time	0.583
Orientation to place	0.175
Registration	0.044
Attention and calculation	-0.010
Recall	0.643
Language	0.153
Drawing	0.168

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 32. The results of the structure matrix in the healthy older adults and the patients with MCI (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Orientation to time	0.688
Recall	0.648
Orientation to place	0.500
Language	0.361
Attention and calculation	0.346
Drawing	0.223
Registration	0.115

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; AD, Alzheimer's Disease; 1, Normal vs. AD.

Table 33. Classification rates (%) by discriminant analysis in healthy older adults and the patients with AD (K-MMSE)

		Predictive groups		
	Groups	Normal	AD	Total
Frequency	Normal	87	4	91
	AD	5	92	97
%	Normal	95.6	4.4	100.0
	AD	5.2	94.8	100.0
Classification accuracy				95.2%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; AD, Alzheimer's Disease.

Table 34. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the healthy older adults compared with the patients with MCI

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV*	14/15	0.708 [0.644, 0.773]	60%	75%
MMSE-2:SV [†]	26/27	0.720 [0.655, 0.785]	74%	59%
MMSE-2:EV [‡]	46/47	0.728 [0.662, 0.795]	71%	69%
K-MMSE	26/27	0.703 [0.638, 0.768]	70%	59%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examinaion-2: Brief Version; MMSE-2:SV, MMSE-2:Standard Version; MMSE-2:EV, MMSE-2:Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment.

Note.

* $p = 0.866$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.458$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.406$ for MMSE-2:EV vs. K-MMSE.

Table 35. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the patients with MCI compared with the patients with AD

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV*	11/12	0.930 [0.900, 0.961]	88%	87%
MMSE-2:SV [†]	23/24	0.925 [0.894, 0.956]	84%	87%
MMSE-2:EV [‡]	36/37	0.921 [0.893, 0.949]	82%	85%
K-MMSE	23/24	0.936 [0.910, 0.961]	84%	88%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; MMSE-2:SV, MMSE-2: Standard Version; MMSE-2:EV, MMSE-2: Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

* $p = 0.705$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.273$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.181$ for MMSE-2:EV vs. K-MMSE.

Table 36. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the healthy older adults compared with the patients with AD

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV	10/11	0.973 [0.955, 0.992]	98%	70%
MMSE-2:SV	23/24	0.952 [0.921, 0.983]	92%	87%
MMSE-2:EV	34/35	0.943 [0.907, 0.980]	92%	71%
K-MMSE	23/24	0.971 [0.950, 0.993]	93%	88%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; MMSE-2:SV, MMSE-2: Standard Version; MMSE-2:EV, MMSE-2: Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; AD, Alzheimer's Disease.

Note.

* $p = 0.861$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.084$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.068$ for MMSE-2:EV vs. K-MMSE.

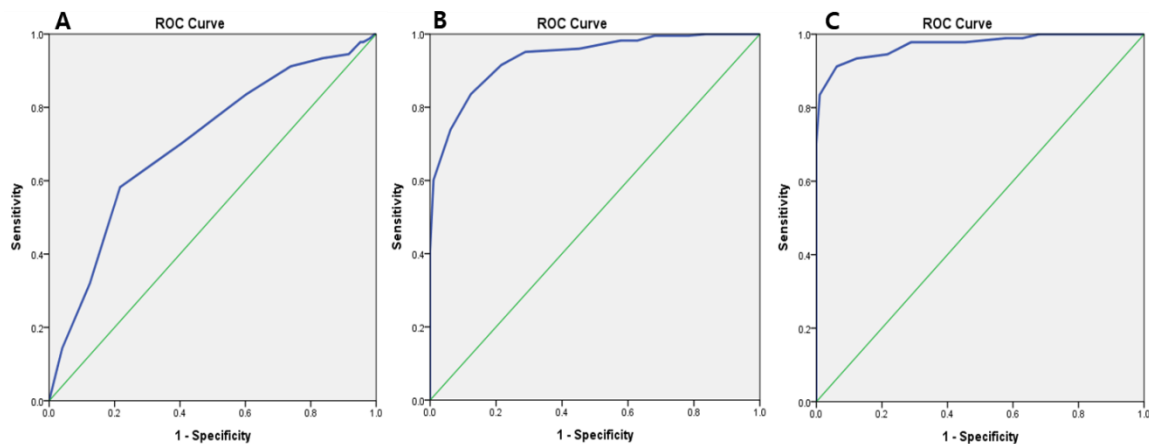


Figure 1. Korean version of the Mini-Mental State Examination (K-MMSE). Receiver operator characteristic (ROC) curve analysis of the K-MMSE in the groups of normal, mild cognitive impairment (MCI), and Alzheimer's Disease (AD). (A) Normal vs. MCI, Area Under the Curve (AUC) = 0.70. (B) MCI vs. AD, Area Under the Curve (AUC) = 0.94. (C) Normal vs. AD, Area Under the Curve (AUC) = 0.97.

Study 3

Comparison between the Anatomic Correlation of the Mini-Mental State Examination and the Mini-Mental State Examination-2: A Voxel-Based Morphometric Study in the Patients with Mild Cognitive Impairment and Alzheimer' s Disease in Korea

Introduction

In studies 1 and 2, the reliability and validity of the newly developed MMSE-2 were analyzed in the patients with MCI and AD, and the sensitivity and specificity of the MMSE-2 were high so it has been shown that it can be used clinically as a cognitive screening test in Korea. In addition, as a result of analyzing the difference between the

K-MMSE and the MMSE-2, the MMSE-2:SV and the MMSE-2:EV were more sensitive to discriminate between the healthy older adults and the patients with MCI than the K-MMSE, and the K-MMSE and the MMSE-2:BV could be used more usefully as dementia progressed. Therefore, the MMSE-2 is found to be more useful in the clinical setting depending on the group of the patients as a cognitive screening test.

In study 3, the purpose of this study is to examine the correlations between the total scores of the MMSE-2 and the K-MMSE with global volume changes in cortical gray matter measured by structural magnetic resonance imaging (MRI) using voxel-based morphometry (VBM).

As mentioned earlier, as AD progresses, the cognitive function of patients has been declined, volume loss in cerebral cortex has been appeared, and the neurotic plaques and neurofibrillary tangles has been accumulated in the brain tissue (Braak et al., 1991; Golde et al., 2000).

In recent years, there have been a number of studies that have analyzed the relationship between the total score of the MMSE and the cortical gray matter volume changes in patients with cognitive decline.

Since the role of the hippocampus, especially in the temporal lobe, is related with episodic memory (Scoville et al., 1957), many studies have examined the relationship between changes of cognitive function of the patients with amnesic MCI and the size of the hippocampus. The previous studies showed that when the relationship between the total score of the MMSE and size of hippocampus in patients with MCI and AD was compared, as the hippocampal atrophy progressed, the total score of the MMSE has been decreased, suggesting that the MMSE would be proved to be a sensitive test for hippocampal atrophy (Yavuz et al., 2007; Laakso et al., 1995; Babiloni et al., 2009).

Jack et al. (1999) reported that the hippocampus of patients with amnesic MCI and AD were atrophied and shrinking and also reported that the size of the hippocampus was important in predicting AD. However, the important features of patients with AD were not only atrophy of hippocampus, but also atrophy of the areas related to the anatomical temporo-parietal network associated with episodic memory. The temporo-parietal network includes the hippocampus including the parahippocampal gyrus, the entorhinal cortex, the retrosplenial area, the

posterior cingulate gyrus, and the precuneus (Buckner, 2004; Walhovd, et al., 2008; Singh et al., 2006).

In a study by Apostolova et al. (2006), the relationship between the total score of the MMSE and structural neuroimaging in 29 patients with AD and 5 patients with amnesic MCI was analyzed. As a result, it was found that the total score of the MMSE and the gray matter integrity in the inner cortex, parahippocampal, precuneus, superior parietal lobule, subgenual cingulate gyrus, and orbitofrontal cortices were strongly correlated. In other words, as the score of MMSE has been decreased, the degree of brain atrophy has been changed severely. Moreover, there was a significant correlation between the total score of the MMSE and the size of gray matter in bilaterally temporal lobe, middle frontal gyrus, left angular gyrus, and supramarginal gyrus. The MMSE was found to be related to the overall size of gray matter of both cerebral hemispheres, particularly in the left hemisphere (Ridha et al., 2007; Sluimer et al., 2008; Hua et al., 2008).

Fjell et al. (2009) also examined the relationship between cerebral cortical thickness measured by brain MRI and the total scores of the MMSE in 96 patients with severe AD and 93 healthy older adults. The results showed that the total score of the MMSE and the size of overall brain, cerebral cortex, accumbens, cerebral white matter, inferior lateral ventricles, and hippocampus were highly correlated. The brain size of the patients with AD was reduced by 58% compared with the healthy older adults.

In addition, there were also a number of the previous studies reporting the relationship between the total score of the MMSE and regional cerebral blood flow (rCBF) (Eberling et al., 1993; DeKosky et al., 1990; Wolfe et al., 1995; Ushijima et al., 2002). In the study of Ushijima et al. (2002), the relationship between the total score of the MMSE and rCBF in 59 patients with AD and 12 healthy older adults was analyzed. CBF was measured using SPECT with N-isopropyl-p- ^{123}I iodoamphetamine autoradiography (Iida et al., 1994). As a result, the total score of the MMSE was significantly correlated with the frontal lobe, medial temporal lobe, and parietal lobe. The results of examining

the relationship between CBF and subtests of the MMSE were as follows. Orientation was related to the parietal lobe and hippocampus, registration was related to the anterior temporal cortex, attention and calculation was related to the frontal lobe, recall was related to the medial temporal lobe, and language was related to the posterior temporal lobe.

Although there have been many studies on the correlation of the MMSE with various brain imaging techniques, there is no study to examine the relationship between the MMSE-2 and global volume changes in cortical gray matter. Therefore, in study 3, the purpose of this study is to examine the correlations between the total scores of the MMSE-2 and the K-MMSE with global volume changes in cortical gray matter measured by structural magnetic resonance imaging (MRI) using voxel-based morphometry (VBM) and to measure how they change with progression of dementia. Moreover, the area of brain that correlates with the newly added story memory test and processing speed test in the MMSE-2 will be investigated.

Materials and Methods

1. Participants

1.1. Patients

Among the patients who participated in study 1, the data of 22 patients with MCI (8 males and 14 females) and 11 patient with AD (5 males, 6 females) who underwent brain MRI within approximately 6 months after examining the MMSE-2 and the K-MMSE were used in this study. They were diagnosed as MCI (CDR 0.5, CDR-SOB 0.5–2.0), early stage of AD (CDR 0.5, CDR-SOB 2.5–4.0), mild stage of AD (CDR 1, CDR-SOB 4.5–9.0), and moderate stage of AD (CDR 2, CDR-SOB 9.5–15.5).

1.2. Control participants

Among the healthy older adults who participated in study 1, the data of 10 healthy older adults (5 males and 5 females) who underwent brain MRI within approximately 6 months after examining the MMSE-2 and the K-MMSE were used in this study.

2. Instruments

2.1. MMSE-2

The description of the MMSE-2 was the same as that of study 1 and 2.

2.2. K-MMSE

The description of the K-MMSE was the same as that of study 1 and 2.

2.3. Data acquisition and analysis

MRI was acquired using T1-weighted three dimensional (3D) volumetric spoiled gradient echo (SPGR) sequences on GE Signa Philips Intera Achieva 3.0T (Philips, Amsterdam, Netherlands). T1-weighted 3D volumetric SPGR sequences were parallel to the midline of the brain and 170–180 consecutive sagittal sections of 1 mm thickness were obtained. The conditions of the image were as follows. We analyzed only the images taken within 6 months after examining the MMSE-2

and the MMSE-2, with TR 8.1 msec, TE 4.6 msec, no interslice gap, FOV 240x240 mm and NEX =1. Images were analyzed by MATLAB 7.6.0 (Mathworks, Natick, MA, USA) and Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). In order to keep each brain size and each anatomical position constant, each brain surface was planted in a standard three-dimensional circular pattern. First, the original images were segmented. Segmentation is a method of classifying the anatomical parts such as gray matter, white matter, and cerebrospinal fluid according to the purpose of the research. Gray matter, white matter, and cerebrospinal fluid were all subdivided, and this was put into 'gray.nii', a basic template in SPM 5, so that gray matter of the brain was placed at a certain position. Differences between the MRIs of each patient were corrected according to the International Consortium for Brain Mapping template for East Asian Brains during normalization, and the bias full width at half maximum (FWHM) was 70 mm. Smoothing was performed (12mm FWHM isotropic Gaussian kernel) to minimize gray matter variation. Thus, a cortical image of a certain size was obtained in accordance with the

purpose of the study. Multiple regression analysis was used to compare the gray matter of brain with the patients with MCI, the patients with AD, and the healthy older adults after correcting age and educational level as covariates. The estimated threshold value for each region was set to be $p = 0.005$, and the voxel extent threshold was 100. After comparing the data among the patients with MCI, the patients with AD, and the healthy older adults (uncorrected, $p < 0.005$), and the area of brain atrophy was identified using Talairach Client 2.4.2 (www.talairach.org) so the name of the corresponding gray matter was confirmed.

3. Procedure

The procedure was the same as study 2, and the brain MRI images taken only within 6 months from the date after examining the MMSE-2 and the K-MMSE were selected and analyzed.

4. Statistical analysis

First, an ANOVA was used to compare age and education levels, and a chi square test was used to compare gender across the three groups (22 patients with MCI, 11 patients with AD, and 10 healthy older adults).

Second, the results of the MMSE-2 (BV, SV, and EV) among the three groups were analyzed using an ANCOVA after controlling for age as a covariate.

Third, the results of the K-MMSE among the three groups were analyzed using an ANCOVA after controlling for age as a covariate.

Finally, multiple regression analysis was used to analyze the correlation between the total scores of the MMSE-2 (BV, SV, and EV) and the total score of the K-MMSE and the size of gray matter volume through VBM analysis.

Data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be significant for all analyses, and brain MRI images were also analyzed using MATLAB 7.6.0 and SPM 5 programs.

Results

1. The demographic data in the groups of normal, MCI, and AD

The demographic characteristics of the patients with MCI, the patients with AD, and the healthy older adults are presented in Table 1. The mean age of the patients with MCI was 70.95 ± 7.93 years (range: 56–85 years), and the mean age of the patients with AD was 74.09 ± 6.32 (range: 65–88 years). The mean age of the healthy older adults was 65.60 ± 7.63 years (range: 55–77 years). The mean number of years of education was 11.68 ± 4.36 years (range: 6–18 years) in the patients with MCI, 11.18 ± 4.62 years (range: 6–16 years) in the patients with AD, and 12.50 ± 4.20 years (range: 6–18 years) in the healthy older adults.

There were no significant differences in the participants' gender, $\chi^2(1, 43) = 0.604$, $p = 0.74$, education, $F(2, 40) = 0.241$, $p = 0.79$, but there was significant difference in age, $F(2, 40) = 3.447$, $p < 0.05$, among the three groups. According to Tukey's *post hoc* analysis, the

mean age of the patients with AD was significantly higher than the mean age of the healthy older adults, but there was no significant difference in the mean age between the patients with AD and the patients with MCI or between the patients with MCI and the healthy older adults.

2. The results of the MMSE-2 in the groups of normal, MCI, and AD

2.1. MMSE-2:BV

The MMSE-2:BV scores of the participants in the three groups are shown in Table 2. An ANCOVA that controlled for age revealed significant differences among the three groups on the MMSE-2:BV. According to Tukey's *post hoc* analysis, the scores of orientation to time, orientation to place, and total score of the MMSE-2:BV were significantly higher for the patients with MCI and the healthy older adults than for the patients with AD, but there was no significant difference between the patients with MCI and the healthy older adults.

However, there were no significant differences in the items such as registration and recall in the three groups.

2.2. MMSE-2:SV

The MMSE-2:SV scores of the participants in the three groups are shown in Table 3. An ANCOVA that controlled for age revealed significant differences among the three groups on the MMSE-2:SV. According to Tukey's *post hoc* analysis, the score of attention and calculation was significantly higher for the healthy older adults than for the patients with MCI and AD, and it was significantly higher for the patients with MCI than for the patient with AD. Moreover, the scores of orientation to time, orientation to place, and total score of the MMSE-2:SV were significantly higher for the patients with MCI and the healthy older adults than for the patients with AD, but there were no significant differences between the patients with MCI and the healthy older adults. However, there were no significant differences in the items such as registration, recall, language, and drawing in the three groups.

2.3. MMSE-2:EV

Finally, The MMSE-2:EV scores of the participants in the three groups are shown in Table 4. An ANCOVA that controlled for age revealed significant differences among the three groups on the MMSE-2:EV. According to Tukey's *post hoc* analysis, the scores of attention and calculation, story memory, and total score of the MMSE-2:EV were significantly higher for the healthy older adults than for the patients with MCI and AD, and they were significantly higher for the patients with MCI than for the patient with AD. Moreover, the scores of orientation to time, orientation to place, and processing speed were significantly higher for the patients with MCI and the healthy older adults than for the patients with AD, but there were no significant differences between the patients with MCI and the healthy older adults. However, there were no significant differences in the items such as registration, recall, language, and drawing in the three groups.

3. The results of the K-MMSE in the groups of normal, MCI, and AD

The K-MMSE score of the participants in the three groups are presented in Table 5. An ANCOVA that controlled for age revealed significant differences among the three groups on the K-MMSE. According to Tukey's *post hoc* analysis, the score of attention and calculation was significantly higher for the healthy older adults than for the patients with MCI and AD, and it was significantly higher for the patients with MCI than for the patient with AD. Moreover, the scores of orientation to time, orientation to place, and total score of the K-MMSE were significantly higher for the patients with MCI and the healthy older adults than for the patients with AD, but there were no significant differences between the patients with MCI and the healthy older adults. However, there were no significant differences in the items such as registration, recall, language, and drawing in the three groups.

4. Voxel-based morphometry of gray matter

4.1. MMSE-2

4.1.1. MMSE-2:BV (Table 6; Figure 1)

The gray matter volume reduction and the total score of the MMSE-2:BV in the patients with MCI, the patients with AD, and the healthy older adults were compared. The results showed that the gray matter volume in the left fusiform gyrus and left inferior temporal gyrus of the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

4.1.2. MMSE-2:SV (Table 7; Figure 2)

The gray matter volume reduction and the total score of the MMSE-2:SV in the patients with MCI, the patients with AD, and the healthy older adults were compared. The results showed that the gray matter volume in the right inferior temporal gyrus, left fusiform gyrus, left inferior temporal gyrus, left hippocampus, and right fusiform gyrus of

the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

4.1.3. MMSE-2:EV (Table 8; Figure 3)

The gray matter volume reduction and the total score of the MMSE-2:EV in the patients with MCI, the patients with AD, and the healthy older adults were compared. The results showed that the gray matter volume in the right cuneus, left cuneus, right inferior temporal gyrus, right inferior occipital gyrus, right inferior temporal gyrus, left inferior frontal operculum, left precentral gyrus, left superior temporal pole, right angular gyrus, right medial temporal gyrus, and right fusiform gyrus of the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

4.1.4. MMSE-2:EV- story memory (Table 9; Figure 4)

Among the subtests in the MMSE-2, only the story memory test was analyzed. The gray matter volume reduction and the score of story memory test of the MMSE-2 in the patients with MCI, the patients with

AD, and the healthy older adults were compared. The results showed that the gray matter volume in the right inferior occipital gyrus, left cuneus, left fusiform gyrus, left medial frontal gyrus, right angular gyrus, right medial superior frontal gyrus, right anterior cingulate gyrus, left supramarginal gyrus, left superior temporal gyrus, left inferior frontal operculum, left medial temporal gyrus, and right inferior frontal operculum of the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

4.1.5. MMSE-2:EV- processing speed (Table 10; Figure 5)

Among the subtests in the MMSE-2, only the processing speed test was analyzed. The gray matter volume reduction and the score of processing speed test of the MMSE-2 in the patients with MCI, the patients with AD, and the healthy older adults were compared. The results showed that the gray matter volume in the left cerebellum of the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

4.2. K-MMSE (Table 11; Figure 6)

The gray matter volume reduction and the total score of the K-MMSE in the patients with MCI, the patients with AD, and the healthy older adults were compared. The results showed that the gray matter volume in the left fusiform gyrus, left inferior temporal gyrus, left hippocampus, left cuneus, right inferior temporal gyrus, right fusiform gyrus, left inferior temporal gyrus, left superior occipital gyrus, and left calcarine fissure of the patients with MCI and AD was significantly reduced than the healthy older adults (uncorrected, $p < 0.005$).

Discussion

In study 3, the gray matter volume reduction of the brain was compared with the two tests (MMSE-2 and K-MMSE) using VBM analysis to determine whether the MMSE-2 and the K-MMSE scores correlated with focal brain volume reduction in the patients with MCI and AD.

The results of study 3 were as follows. First, the results of the MMSE-2 (BV, SV, and EV) and the K-MMSE were significantly differed among the three groups (healthy older adults, MCI, and AD). Although there were no significant differences in both the MMSE-2:BV and the MMSE-2:SV between the healthy older adults and the patients with MCI, the scores of the MMSE-2:BV and the MMSE-2:SV for the healthy older adults and the patients with MCI were significantly higher than for the patients with AD. Especially, there were significant differences in the items of the MMSE-2:SV such as orientation to time, orientation to place, and attention and calculation, but there were no significant differences on the items such as registration and recall. Moreover, the scores of the healthy older adults were significantly higher than the

patients of MCI and AD, and the scores of the patients with MCI were significantly higher than the patients with AD in the subtests of the MMSE-2:EV such attention and calculation, and story memory test. These results are consistent with the results of study 1 and 2, and the most discriminating tests are verbal and working memory tests related to episodic memory. Finally, in the K-MMSE, there was no significant difference between the healthy older adults and the patients with MCI, but there was a significant difference between the two groups (healthy older adults and MCI) and the patients with AD. This data is in agreement with the previous study (Kang et al., 1997). Therefore, as shown in studies 1 and 2, the previous results showed that the most sensitive tests that can distinguish the patients with MCI and AD from the healthy older adults are the tests related to episodic memory such as story memory, orientation to time, and orientation to place.

The correlation between the MMSE-2 and gray matter volume reduction of the brain using the VBM analysis was as follows. First of all, the MMSE-2:BV scores correlated positively with gray matter volume in the left fusiform gyrus and left inferior temporal gyrus.

Moreover, the MMSE-2:SV scores correlated positively with gray matter volume in the right inferior temporal gyrus, left fusiform gyrus, left inferior temporal gyrus, left hippocampus, and right fusiform gyrus. Finally, the MMSE-2:EV scores correlated positively with gray matter volume in the right cuneus, left cuneus, right inferior temporal gyrus, right inferior occipital gyrus, right inferior temporal gyrus, left inferior frontal operculum, left precentral gyrus, left superior temporal pole, right angular gyrus, right medial temporal gyrus, and right fusiform gyrus.

According to the results of the previous studies about gray matter atrophy in the patients with MCI and AD, the gray matter atrophy of the patients with MCI was found in the hippocampus, parahippocampal gyrus, anterior cingulate gyrus, middle frontal gyrus, inferior parietal lobule, paracentral gyrus, pars opercularis, posterior cingulate gyrus, superior frontal gyrus, and temporal pole (Chuanming et al., 2011). As the Alzheimer's disease progresses, the area of gray matter atrophy of brain becomes wider. The gray matter atrophy of the patients with AD was found in global area of the temporal and parietal lobes including

the hippocampus, parahippocampal gyrus, entorhinal, retrosplenial area, posterior cingulate gyrus, precuneus cortices, superior parietal lobule, supramarginal gyrus, inferior parietal lobule, and fusiform gyrus (Buckner, 2004; Walhovd et al., 2008; Singh et al., 2006). Furthermore, the gray matter atrophy of the patients with AD was also found in global area of the frontal lobe and the lateral occipital lobe including the superior frontal gyrus, middle frontal gyrus, pars opercularis, frontal pole, precentral gyrus, and lateral orbitofrontal lobe (Fjell et al., 2009).

When we look at the atrophic areas of gray matter associated with the MMSE-2:BV and the MMSE-2:SV, there were many parts that correspond to areas where gray matter volume reduction in the patients with MCI and AD, especially in bilateral temporal lobes. However, the above two tests did not correlate with cerebral gray matter atrophy of the parietal lobe and frontal lobe which were shown in patients with MCI and AD. However, when we look at the atrophic areas of gray matter associated with the MMSE-2:EV, there were a high correlation with the broader area of bilateral temporal lobes, parietal lobe, and frontal lobe.

In addition, the K-MMSE scores correlated positively with gray matter volume in the left fusiform gyrus, left inferior temporal gyrus, left hippocampus, left cuneus, right inferior temporal gyrus, right fusiform gyrus, left inferior temporal gyrus, left superior occipital gyrus, and left calcarine fissure. This data is consistent with the previous studies (Yavuz et al., 2007; Laakso et al., 1995; Babiloni et al., 2009; Jack et al., 1999; Buckner, 2004; Walhovd et al., 2008; Singh et al., 2006, Apostolova et al., 2006; Fjell et al., 2009). However, the K-MMSE was also highly correlated with both parietal and temporal lobes, but not with the frontal lobe.

Thus, it was shown that the MMSE-2:EV evaluated more global brain regions than the MMSE-2:BV, the MMSE-2:SV and the K-MMSE. One of the shortcomings of the MMSE is that it is insensitive to impairment in executive functioning of the frontal lobe (Galasko et al., 1994; Kang et al., 1997), but the MMSE-2:EV can evaluate executive function of the frontal lobe, unlike the MMSE, so it can be thought that the MMSE-2:EV can evaluate more accurately about the overall cognitive functioning of the patients.

In the following, among the subtests of the MMSE-2:EV, the correlation between the story memory test, which is the most sensitive test to discriminate the patients with MCI and AD from the healthy older adults, and the atrophy of cortical gray matter was analyzed separately. The results showed that scores of the story memory test in the MMSE-2:EV correlated positively with the right inferior occipital lobe, left cuneus, left fusiform gyrus, left medial frontal gyrus, right angular gyrus, right medial superior frontal gyrus, right anterior cingulate gyrus, left supramarginal gyrus, left superior temporal gyrus, left inferior frontal operculum, left medial temporal gyrus, and right inferior frontal operculum. In other words, the story memory test was found to be associated with bilateral temporal, frontal, and parietal lobes as a whole.

Nolde et al. (1998) examined the relationship between the story memory test and the prefrontal cortex through functional magnetic resonance imaging (fMRI). The results showed that both prefrontal functions were activated when recalling the story. In more detail, when recalling the story in detail, only the left prefrontal lobe was activated,

and when the story was recalled by simplification or integration, the right prefrontal lobe was activated.

The existing researches on information processing of story recall were as follows. According to Hudon et al. (2006), when we looked at information processing when we recalled a story, the important and big proposition of the story was stored at first and then the detailed or less important part of the story was stored. Moreover, when people remembered the story, they seemed to remember more topics than the details of the story (Meyer, 1975). In other words, rather than remembering each word in the story, people usually tend to memorize the whole theme of the story. In addition, a comparison of storytelling tests between young adults and older adults with normal cognitive functioning revealed that young adults were more likely to remember more information than elderly people, but there was no difference in remembering the subject of the story (Hulstsch et al., 1984). According to O'Donnell, et al. (1988), remembering the story was required the ability to manage stories in terms of time flow and logical evolution

and to integrate and organize thinking, so it is said that the overall cognitive function was measured.

Therefore, when memorizing a story, it is necessary to memorize the whole meaning of the words composing the story rather than to memorize each one of them, and to remember the common sense and the stories related to it so it may be related to the whole brain area rather than the hippocampus, and it is presumed to be related not only to the left temporal lobe but also the right temporal lobe and the frontal lobe. In other words, it is believed that the story memory test is related to the whole brain function as it is known.

In addition, the processing speed test has been found to be associated with the left cerebellum. The symbol-digit coding test is a tool to measure psychomotor ability, visual searching, and attention ability associated with executive function of the frontal lobe (Folstein et al., 2010). The processing speed test is similar to the symbol digit modality test (SDMT) (Smith, 1982). In the fMRI study, 18 normal subjects were examined for their relationship to the brain area associated with SDMT, and the fronto-parieto-occipital network, caudate

nucleus, and cerebellum were activated (Forn et al., 2009). The cerebellum is mainly related to the information processing related to the cognitive function as well as the control of motor capacity related to the sensorimotor function (Habas et al., 2009; Krienen et al., 2009; O'Reilly et al., 2010). Therefore, it can be thought that there might be a connection between cerebellum and the processing speed test which evaluates psychomotor ability.

Therefore, the overall results of this study suggested that the MMSE-2 was more related to the degree of atrophy of the general brain area than to the K-MMSE. In particular, the MMSE-2:EV can be more useful as a cognitive screening test in clinical settings because the MMSE-2:EV has the highest correlation with overall brain area and can measure the frontal lobe function which cannot be measured by the K-MMSE.

Table 1. Characteristics of participants (M±SD)

	All participants (n=43)		
	Normal (n=10)	MCI (n=22)	AD (n=11)
Age (years)	65.60±7.63	70.95±7.93	74.09±6.32*
Education (years)	12.50±4.20	11.68±4.36	11.18±4.62
Male/Female	5/5	8/14	5/6

Abbreviations: M, Mean; SD, Standard deviation; MCI, Mild Cognitive impairment; AD, Alzheimer's disease.

Note.

* $p < 0.001$ for Normal vs. AD.

Table 2. The results of the MMSE-2:BV in the groups of normal, MCI, and AD (M \pm SD)

MMSE-2:BV	N(1)	MCI(2)	AD(3)	F	<i>df</i>	η^2	<i>Post-hoc</i>
Registration	3.00 \pm 0.00	2.95 \pm 0.21	2.73 \pm 0.47	2.276	2, 39	0.105	1=2=3
Orientation to time	4.70 \pm 0.48	4.59 \pm 0.59	2.64 \pm 1.21	23.000*	2, 39	0.541	1=2>3
Orientation to place	5.00 \pm 0.00	4.59 \pm 0.59	3.36 \pm 1.12	13.546*	2, 39	0.410	1=2>3
Recall	1.40 \pm 1.08	1.14 \pm 0.89	0.64 \pm 0.92	1.109	2, 39	0.054	1=2=3
Total score	14.10 \pm 1.37	13.27 \pm 1.39	9.27 \pm 2.72	18.96*	2, 39	0.493	1=2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.001$.

Table 3. The results of the MMSE-2:SV in the groups of normal, MCI, and AD (M±SD)

MMSE-2:SV	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Registration	3.00±0.00	2.95±0.21	2.73±0.47	2.276	2, 39	0.105	1=2=3
Orientation to time	4.70±0.48	4.59±0.59	2.64±1.21	23.000*	2, 39	0.541	1=2>3
Orientation to place	5.00±0.00	4.59±0.59	3.36±1.12	13.546*	2, 39	0.410	1=2>3
Recall	1.40±1.08	1.14±0.89	0.64±0.92	1.109	2, 39	0.054	1=2=3
Attention and Calculation	4.70±0.68	3.45±1.37	2.27±1.49	5.719 [†]	2, 39	0.227	1>2>3
Language	7.90±0.32	7.68±0.57	7.36±1.21	0.566	2, 39	0.028	1=2=3
Drawing	1.00±0.00	0.77±0.43	0.64±0.51	0.726	2, 39	0.036	1=2=3
Total Score	27.70±1.83	25.23±2.72	19.55±4.57	14.553*	2, 39	0.427	1=2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:SV, Mini-Mental State Examination-2:Standard Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.001$.

[†] $p < 0.01$.

Table 4. The results of the MMSE-2:EV in the groups of normal, MCI, and AD (M±SD)

MMSE-2:EV	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Registration	3.00±0.00	2.95±0.21	2.73±0.47	2.276	2, 39	0.105	1=2=3
Orientation to time	4.70±0.48	4.59±0.59	2.64±1.21	23.000*	2, 39	0.541	1=2>3
Orientation to place	5.00±0.00	4.59±0.59	3.36±1.12	13.546*	2, 39	0.410	1=2>3
Recall	1.40±1.08	1.14±0.89	0.64±0.92	1.109	2, 39	0.054	1=2=3
Attention and Calculation	4.70±0.68	3.45±1.37	2.27±1.49	5.719 ⁺	2, 39	0.227	1>2>3
Language	7.90±0.32	7.68±0.57	7.36±1.21	0.566	2, 39	0.028	1=2=3
Drawing	1.00±0.00	0.77±0.43	0.64±0.51	0.726	2, 39	0.036	1=2=3
Story memory	11.30±2.95	6.59±3.14	3.27±1.49	16.061*	2, 39	0.452	1>2>3
Processing speed	13.30±4.14	10.27±4.29	6.18±3.46	4.477*	2, 39	0.187	1=2>3
Total Score	52.30±8.21	42.14±8.40	29.00±6.99	16.736*	2, 39	0.462	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; MMSE-2:EV, Mini-Mental State Examination-2:Expanded Version; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

* $p < 0.001$.

⁺ $p < 0.01$.

Table 5. The results of the K-MMSE in the groups of normal, MCI, and AD (M±SD)

K-MMSE	N(1)	MCI(2)	AD(3)	F	df	η^2	Post-hoc
Orientation to time	4.70±0.48	4.59±0.59	2.64±1.21	23.000*	2, 39	0.541	1>2>3
Orientation to place	5.00±0.00	4.59±0.59	3.36±1.12	13.546*	2, 39	0.410	1=2>3
Registration	3.00±0.00	3.00±0.00	3.00±0.00				
Attention and Calculation	4.70±0.68	3.45±1.37	2.27±1.49	5.719*	2, 39	0.227	1>2>3
Recall	1.50±0.85	1.09±1.19	0.18±0.41	2.947	2, 39	0.131	1=2=3
Language	8.00±0.00	7.59±0.80	7.27±1.19	0.804	2, 39	0.040	1=2=3
Drawing	1.00±0.00	0.77±0.43	0.64±0.51	0.726	2, 39	0.036	1=2=3
Total Score	27.90±1.29	25.09±3.32	19.36±4.32	14.050*	2, 39	0.419	1=2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; K-MMSE, Korean version of the Mini-Mental State Examination; 1, Normal; 2, Mild Cognitive Impairment; 3, Alzheimer's Disease.

Note.

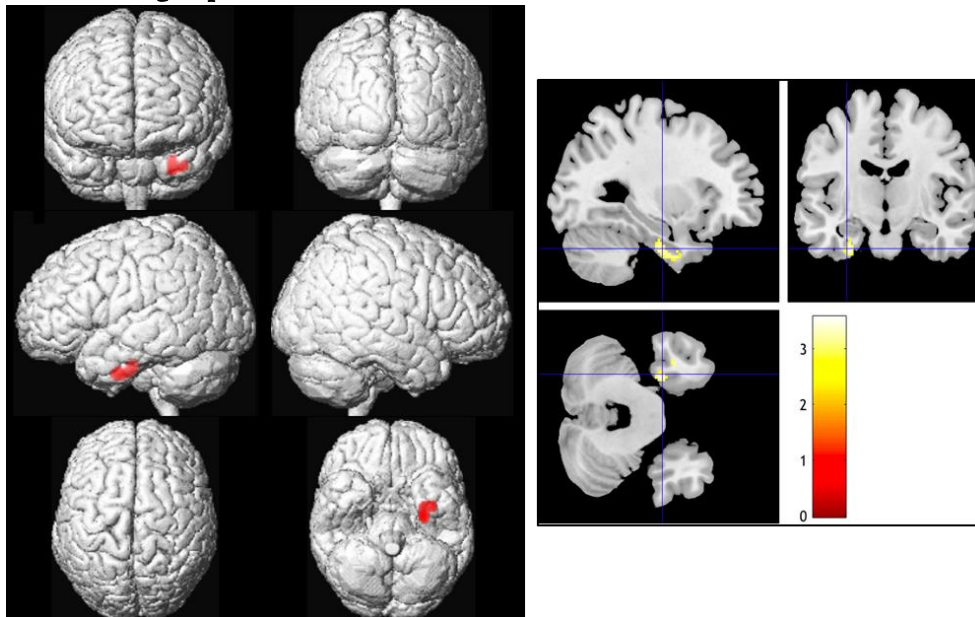
* $p < 0.01$.

Table 6. The correlation of the MMSE-2:BV and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
-28	-12	-32	Left fusiform gyrus	3.30
-36	-2	-34	Left inferior temporal gyrus	3.25

Abbreviations: MMSE-2:BV, Mini-Mental State Examination-2: Brief version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Figure 1. The area of gray matter volume reduction correlated with the MMSE-2:BV in the groups of normal, MCI, and AD



Abbreviations: MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

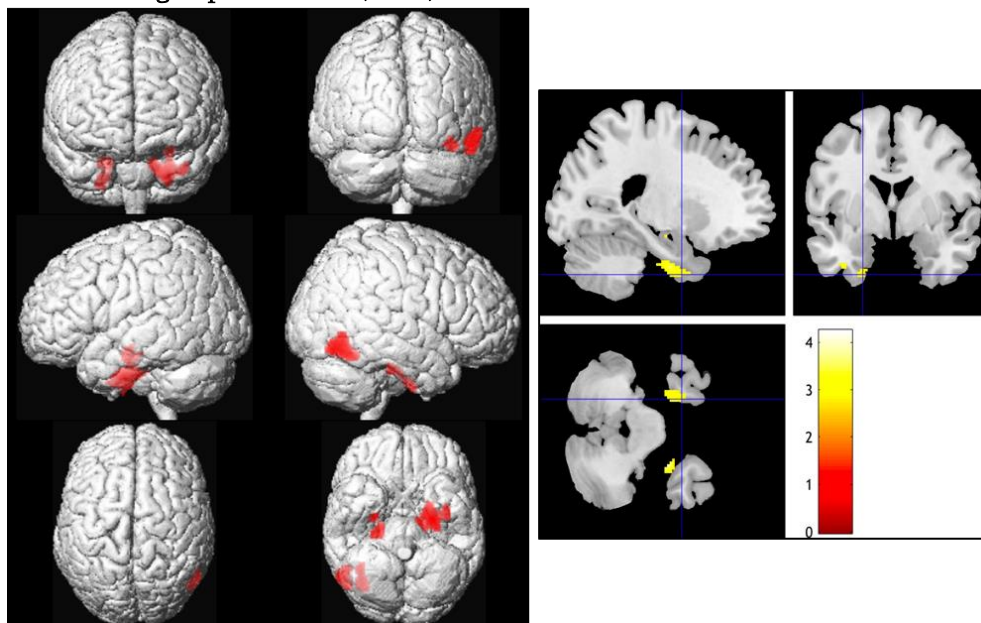
Uncorrected $p < 0.005$.

Table 7. The correlation of the MMSE-2:SV and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
54	-66	-12	Right inferior temporal gyrus	3.83
-28	-14	-34	Left fusiform gyrus	3.64
-38	-4	-34	Left inferior temporal gyrus	3.51
-28	-8	-18	Left hippocampus	3.25
38	-54	-18	Right fusiform gyrus	3.23
38	-66	-16	Right fusiform gyrus	3.16

Abbreviations: MMSE-2:SV, Mini-Mental State Examination-2:Standard version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Figure 2. The area of gray matter volume reduction correlated with the MMSE-2:SV in the groups of normal, MCI, and AD



Abbreviations: MMSE-2:SV, Mini-Mental State Examination-2:Standard version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

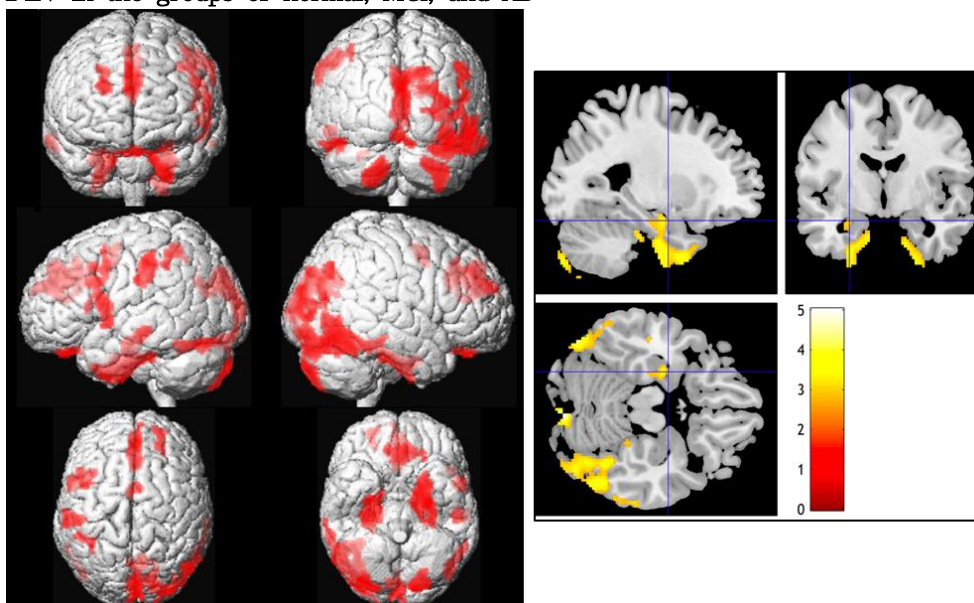
Uncorrected $p < 0.005$.

Table 8. The correlation of the MMSE-2:EV and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
16	-80	36	Right cuneus	4.38
2	-82	28	Left cuneus	4.32
54	-64	-12	Right inferior temporal gyrus	4.11
38	-86	-12	Right inferior occipital gyrus	4.03
50	-54	-20	Right inferior temporal gyrus	3.66
-58	10	14	Left inferior frontal operculum	4.02
-44	6	42	Left precentral gyrus	3.90
-56	6	0	Left superior temporal pole	3.69
48	-70	40	Right angular gyrus	3.91
52	-74	22	Right medial temporal gyrus	3.05
24	-36	-18	Right fusiform gyrus	2.75

Abbreviation: MMSE-2:EV, Mini-Mental State Examination-2:Expanded version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Figure 3. The area of gray matter volume reduction correlated with the MMSE-2:EV in the groups of normal, MCI, and AD



Abbreviations: MMSE-2:EV, Mini-Mental State Examination-2:Expanded version; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

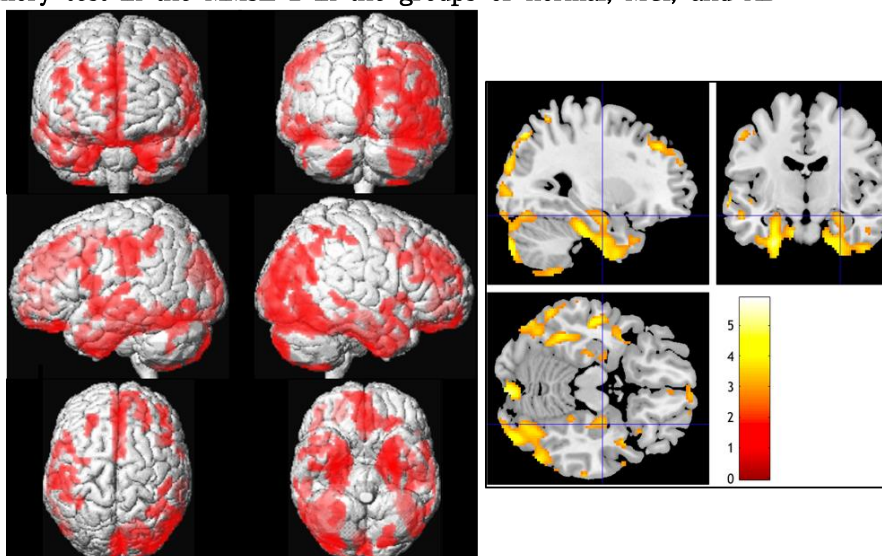
Uncorrected $p < 0.005$.

Table 9. The correlation of the story memory test in the MMSE-2 and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
40	-84	-12	Right inferior occipital lobe	4.96
2	-82	30	Left cuneus	4.59
-28	-12	-36	Left fusiform gyrus	4.56
-26	38	46	Left medial frontal gyrus	4.29
36	-56	42	Right angular gyrus	4.19
4	44	36	Right medial superior frontal gyrus	4.14
6	50	26	Right anterior cingulate gyrus	3.95
-62	-26	34	Left supramarginal gyrus	4.08
-60	4	-8	Left superior temporal gyrus	4.07
-60	10	14	Left inferior frontal operculum	4.03
-52	-20	-14	Left medial temporal gyrus	3.95
50	16	34	Right inferior frontal operculum	3.88

Abbreviation: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease

Figure 4. The area of gray matter volume reduction correlated with the story memory test in the MMSE-2 in the groups of normal, MCI, and AD



Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

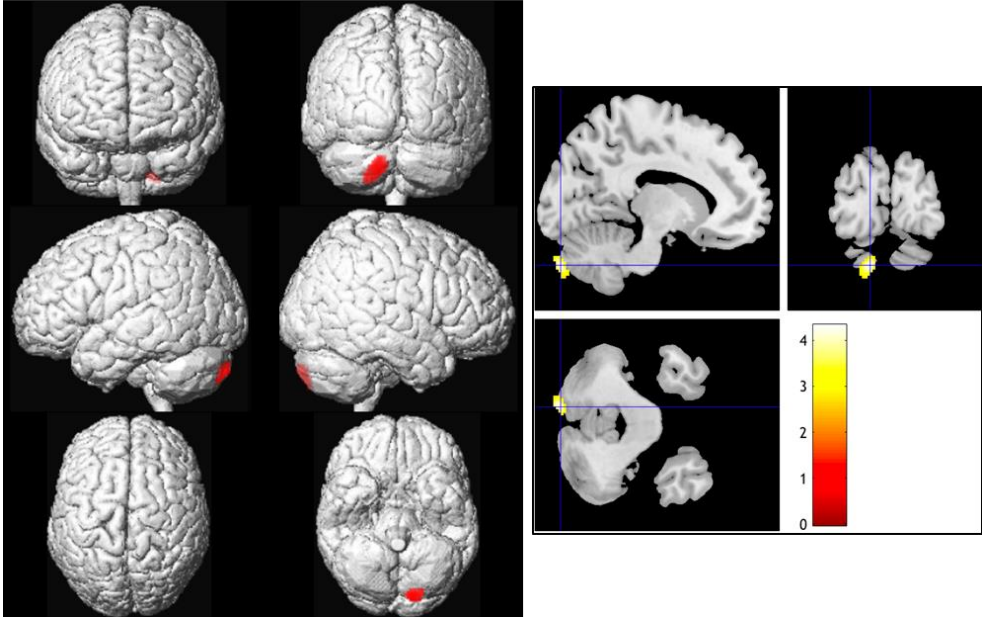
Uncorrected $p < 0.005$.

Table 10. The correlation of the processing speed test in the MMSE-2 and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
-14	-88	-38	Left cerebellum	3.89

Abbreviation: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer’s Disease.

Figure 5. The area of gray matter volume reduction correlated with the processing speed test in the MMSE-2 in the groups of normal, MCI, and AD



Abbreviations: MMSE-2, Mini-Mental State Examination-2; MCI, Mild Cognitive Impairment; AD, Alzheimer’s Disease.

Note.

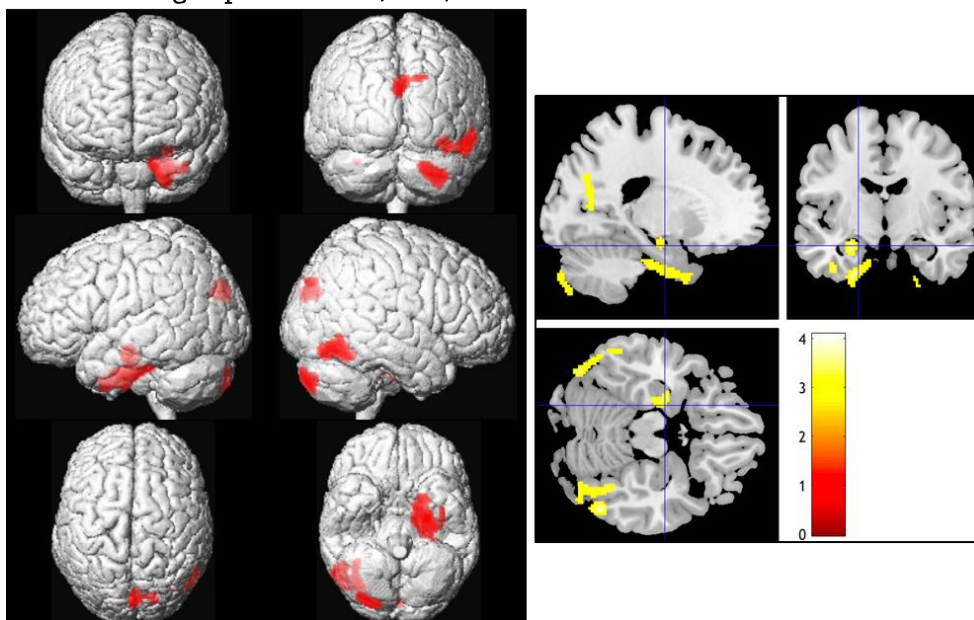
Uncorrected $p < 0.005$.

Table 11. The correlation of the K-MMSE and area of gray matter volume reduction in the groups of normal, MCI, and AD

Coordinates x, y, z			Area of gray matter volume reduction	z-score
-26	14	-34	Left fusiform gyrus	3.71
-40	-6	-34	Left inferior temporal gyrus	3.39
-26	-8	-18	Left hippocampus	3.30
2	-82	28	Left cuneus	3.61
54	-62	-14	Right inferior temporal gyrus	3.55
36	-72	-16	Right fusiform gyrus	3.52
-60	-48	-20	Left inferior temporal gyrus	2.95
-18	-70	30	Left superior occipital gyrus	3.11
-18	-64	10	Left calcarine fissure	2.87

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Figure 6. The area of gray matter volume reduction correlated with the K-MMSE in the groups of normal, MCI, and AD



Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease.

Note.

Uncorrected $p < 0.005$.

Study 4

The Validity and Reliability of the Mini-Mental State Examination-2 for Detecting Vascular Mild Cognitive Impairment and Vascular Dementia in a Korean Population

Introduction

In study 1, the validity and reliability of the MMSE-2 were verified and shown to be useful clinically as a cognitive screening test in Korea.

In study 2, the K-MMSE which has been widely used in Korea as a cognitive screening test and the MMSE-2 were compared to verify which test was more sensitive to discriminate the patients with dementia from the healthy older adults. The results showed that the MMSE-2:SV and MMSE-2:EV were more sensitive to discriminate the healthy older adults from the patients with MCI than the K-MMSE, and

as the dementia progressed, the K-MMSE or the MMSE-2:BV could be used more usefully in the clinical settings. Therefore, the MMSE-2 can be used more effectively than the K-MMSE as a cognitive screening test in clinical settings.

In study 3, the gray matter volume reduction of the brain was compared with the two tests (MMSE-2 and K-MMSE) using VBM analysis to determine whether the MMSE-2 and the K-MMSE scores correlated with focal brain volume reduction in the patients with MCI and AD. The MMSE-2 was more related to the degree of atrophy of the overall brain area than to the K-MMSE. In particular, the MMSE-2:EV had the highest correlation with the general brain area, and also it could measure the frontal lobe function that could not be measured by the K-MMSE.

As mentioned earlier, one of the shortcomings of the MMSE was that there were limited items to evaluate visuospatial and executive functions in the MMSE so it could not accurately distinguish the patients with fronto-temporal dementia or VD from the healthy older adults (Galasko et al., 1994; Tangalos et al., 1996; Romàn et al., 1993;

Mungas et al., 2000; Kang et al., 1997). In addition, Nys et al. (2005) studied the validity of the MMSE in acute stroke patients. According to the result of ROC curve analysis, the AUC of the MMSE was 0.67 ($p = 0.13$) which did not discriminate sensitively between the healthy older adults and the patients with acute stroke. The reason for this was the lack of items to measure the frontal lobe functions such as abstract reasoning, executive functioning, and visual perception/construction ability among the items in the MMSE. In a study by Dong et al. (2010), the Montreal Cognitive Assessment (MoCA) which is one of the cognitive screening tests and the MMSE were compared to verify which test was more sensitive to discriminate the patients with VCI after acute stroke from the healthy older adults. They insisted that the MOCA was more sensitive to discriminate the patients with VD from the healthy older adults than the MMSE because there were the items to evaluate the frontal lobe functions such as executive function, attention, and delayed recall in the MoCA.

As noted in the previous studies, in the MMSE-2 (Folstein et al., 2010), there are subtests for measuring the frontal lobe function, such

as story memory and processing speed tests, so it can be thought that the MMSE-2 may be more sensitive to cognitive decline in the patients with VCI than the MMSE (Folstein et al., 1975).

Therefore, in study 4, the purpose of this study is to evaluate the validity and reliability of the MMSE-2 for assessing the patients with VaMCI and VD in a Korean population. Specifically, we would like to focus on the usefulness of the MMSE-2 as a sensitive screening measure for detecting early cognitive change of the patients with VCI, which has not been detectable via the MMSE.

Materials and Methods

1. Participants

1.1. Patients

Participants who were all over 50 years of old age in this study included 66 patients (36 male, 30 female) with VaMCI and 46 patients (29 male, 17 female) with VD who were recruited from the Clinical Neuroscience Center at the Seoul National University Bundang Hospital from November 2015 to March 2017. They were underwent a medical examination via an interview, a neurological examination, blood tests, brain imaging with CT or MRI, and neuropsychological assessments to obtain a diagnosis. The patients with VaMCI were diagnosed as ‘probable VaMCI’ according to AHA-ASA (American Heart Association–American Stroke Association) (Gorelick et al., 2011), and the patients with VD were diagnosed with the criteria for ‘probable VD’ from NINCDS–AIREN (National Institute of Neurological Disorders and Stroke and the association Internationale pour la Recherche et l’enseignement en Neurosciences) (Román et al., 1993). Moreover, based on the Clinical

Dementia Rating (CDR) (Morris, 1993) and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) (O'Bryant et al., 2008; O'Bryant et al., 2010) scores, patients were classified as having VaMCI (CDR 0.5, CDR-SOB 0.5-2.5) and VD (CDR 0.5 to CDR 2, CDR-SOB 3.0 to 15.5).

1.2. Control participants

The normal control group consisted of 75 healthy (29 Male, 46 female) older adults who were all over 50 years of old age participated in this study from November 2015 to March 2017. They were either the caregivers for one of the patients undergoing treatment at Seoul National University Bundang Hospital, or they were recruited from a health care center. They did not have subjective memory complaints, any of 29 exclusionary diseases, or a history suggestive of a decrease in cognitive function (Christensen et al., 1997). They also had scores that were higher than or at most one standard deviation below the mean scores of the respective age- and education-matched population on the K-MMSE (Kang et al., 1997) and had an average score of 0.42 or lower on the Korean Instrumental Activities of Daily Living (K-IADL)

(Kang et al., 2002). This score has been found to discriminate dementia from normal cognitive aging. The K-IADL is an 11-item questionnaire that includes IADLs of shopping, mode of transportation, ability to handle finances, housekeeping, food preparation, ability to use a telephone, taking medication, recent memory, hobbies, watching television, and fixing. All participants were determined to be free of cognitive deficits, and they all consented to participate in this study. Moreover, all participants were free from neurological or psychiatric illnesses, underwent the same neuropsychological assessments as the cognitively impaired subjects and were included in the healthy control group.

2. Instruments

2.1. MMSE-2

The description of the MMSE-2 was the same as that of study 1.

2.2. Other neuropsychological assessments

To measure the correlation of the MMSE-2 with other neuropsychological assessments, a variety of cognitive functions, such as attention, verbal memory, visuospatial function ability, executive function, and language function, were measured. Attention was assessed using the Korean-Trail Making Test-Elderly's version: Part A (K-TMT-E: type A) (Yi et al, 2007). Verbal memory was assessed using the Seoul Verbal Learning Test (SVLT) (Kang et al., 2003), and a copy of the Rey Complex Figure Test (RCFT) (Meyers et al., 1995) was used to assess visuospatial function. Neuropsychological assessments primarily associated with executive function, including the Korean-Trail Making Test-Elderly's version: Part B (K-TMT-E: Part B) (Yi et al., 2007), the Semantic Word Fluency Test (SWF)-Animal and the Phonemic Word Fluency Test (PWF) (Kang et al., 2000), and the Digit Symbol Coding (DSC) (Joy et al., 2004) were used. Naming ability was assessed using the Korean version of the Boston Naming Test (K-BNT) (Kim et al., 1997). Depression was assessed using the Short version of the Geriatric Depression Scale (SGDS) (Cho et al., 1999). Global measurements, including the K-MMSE (Kang et al., 1997), CDR (Morris, 1993), and

CDR-SOB (O'Bryant et al., 2008; O'Bryant et al., 2010), were also conducted.

3. Procedure

In study 1, because the equivalence of the blue and red forms of the MMSE-2 was high for all three alternative forms: the MMSE-2:BV ($r = 0.90$, $p < 0.01$), the MMSE-2:SV ($r = 0.97$, $p < 0.01$), and the MMSE-2:EV ($r = 0.97$, $p < 0.01$), half of the patients who participated in this study completed the red form of the MMSE-2, and the other half of the patients completed the blue form of the MMSE-2. Moreover, the order in which the neuropsychological assessments were administered is presented in Table 1.

4. Statistical analysis

An analysis of variance (ANOVA) was used to compare age and education levels, and a chi-square test was used to compare gender across all three groups. The results of the neuropsychological tests

including the K-MMSE, among the three groups were analyzed using an analysis of covariance (ANCOVA) after controlling for demographic variables (age, education, and gender). Moreover, the MMSE-2 scores of all three groups were analyzed with an ANCOVA followed by Tukey' s test for *post-hoc* analysis.

Reliability was assessed through measurements of internal consistency, test-retest reliability, and interrater reliability. The internal consistency of the MMSE-2 was measured using Cronbach' s α coefficient. To assess test-retest reliability, the MMSE-2 was re-administered one to two months (31.35 ± 7.53 days) after the initial test to 11 patients with VaMCI, 5 patients with VD, and 4 healthy older adults, and the data were analyzed using Pearson' s correlation coefficients. Interrater reliability was calculated between two neuropsychologists (n=32) using the intraclass correlation coefficient (ICC).

Finally, the validity of the MMSE-2 was analyzed as follows. To assess the concurrent validity of the MMSE-2, Pearson' s correlation coefficient was used to compare the MMSE-2 with the K-MMSE, the SVLT, the copy test of RCFT, the SWF-animal, the PWF, the K-TMT-E:

Part A & B, the DSC, and the K-BNT. To verify the discriminant validity based on the severity of dementia, all participants were classified into five groups according to CDR and CDR-SOB, and the average scores of the MMSE-2 were compared among these five groups using an ANCOVA. To evaluate the diagnostic utility of the MMSE-2, the sensitivity and specificity of the MMSE-2 was examined using a receiver operating characteristics (ROC) curve and area under the curve (AUC) measurements. Data were analyzed using IBM SPSS 22.0. (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be significant for all analyses.

Results

1. The participants' demographic data

The demographic data are presented in Table 2. A total of 187 elderly participants (94 men and 93 women) were enrolled in this study. The mean age of the patients with VaMCI was 71.97 ± 7.67 years (range: 54-91 years), and the mean age of the patients with VD was 72.59 ± 7.35 (range: 54-85 years). The mean age of the healthy older adults was 68.59 ± 7.10 years (range: 50-84 years). The mean number of years of education was 11.06 ± 3.91 years (range: 6-20 years) in the patients with VaMCI, 10.61 ± 3.62 years (range: 6-20 years) in the patients with VD, and 12.49 ± 4.03 years (range: 6-20 years) in the healthy older adults.

There was significant difference in the participants' gender, $\chi^2(1,187) = 7.52$, $p = 0.02$, age, $F(2, 184) = 5.57$, $p < 0.004$, and education, $F(2, 184)=4.07$, $p < 0.019$, among the three groups. According to Tukey' s *post hoc* analysis, the mean age of the patients with VD was significantly higher than that of the healthy older adults, and the mean

age for the patients with VaMCI was significantly higher than that of the healthy older adults. However, there was no significant difference in the mean of age for the patients with VaMCI and the patients with VD. Moreover, the mean number of years of education for the healthy older adults was significantly higher than that of the patients with VD, and there was no significant difference in the mean number of years of education between the patients with VD and the patients with VaMCI or between the patients with VaMCI and the healthy older adults. In addition, the rate of gender for the healthy older adults was significantly different than that of the patients with VD, but there was no significant difference in the rate of gender between healthy older adults and the patients with VaMCI or between the patients with VaMCI and the patients with AD.

2. The results of participants' neuropsychological assessments

The results of the neuropsychological assessments of the three groups (VaMCI, VD, and healthy older adults) were compared. With respect to each of the cognitive domain scores, the three groups differed significantly in each of the domain assessed: attention, verbal memory, visuospatial function, language function, and frontal/executive function (all $p < 0.001$). Tukey's *post hoc* analysis of the cognitive domain revealed that the scores of the healthy older adults were significantly higher than the scores of the patients with VaMCI and VD and that the scores of the patients with VaMCI were significantly higher than the scores of the patients with VD in the K-MMSE, the SVLT, the copy of the RCFT, the K-TMT-E: Part B, the SWF-animal, the PWF, the K-BNT, and the DSC. However, in the K-TMT-E: Part A, although there was no significant difference between the healthy older adults and the patients with VaMCI, the scores of the two groups (healthy older adults and VaMCI) were significantly higher than those of the patients with VD. Moreover, there was no significant difference among the three groups in the SGDS. The mean scores of the subtests

for each group and the results of Tukey' s *post-hoc* analysis are presented in Table 3.

3. The results of the MMSE-2 in the groups of normal, VaMCI, and VD

3.1. MMSE-2:BV

The MMSE-2:BV scores of the participants in the three groups are presented in Table 4. An ANCOVA that controlled for age, education, and gender revealed significant differences among the three groups on the MMSE-2:BV. According to Tukey' s *post hoc* analyses, the total score of the MMSE-2:BV was significantly higher for the healthy older adults than for the patients with VaMCI and the patients with VD, and it was significantly higher for the patients with VaMCI than for the patients with VD. Especially, among all items of the MMSE-2:BV, the score of recall was significantly higher for the healthy older adults than for the patients with VaMCI and the patients with VD, and it was significantly higher for the patients with VaMCI than for the patients

with VD. However, there were no significant differences in the items registration, orientation to time, and orientation to place between the healthy older adults and the patients with VaMCI, but the scores of the three items in the MMSE-2:BV were significantly higher for the healthy older adults and the patients with VaMCI than for the patients with VD.

3.2. MMSE-2:SV

The MMSE-2:SV scores of the participants in the three groups are shown in Table 5. An ANCOVA that controlled for age, education, and gender revealed significant differences among the three groups on the MMSE-2:SV. Tukey' s *post hoc* analyses showed that the total score of the MMSE-2:SV was significantly higher for the healthy older adults than for the patients with VaMCI and the patients with VD, and it was also significantly higher for the patients with VaMCI than for the patients with VD. Particularly, among all items of the MMSE-2:SV, the scores of recall, attention and calculation, and language were significantly higher for the healthy older adults than for the patients with VaMCI and the patients with VD, and they were also significantly

higher for the patients with VaMCI than for the patients with VD. However, there were no significant differences in the items registration, orientation to time, orientation to place, and drawing between the healthy older adults and the patients with VaMCI, but the scores of four items on the MMSE-2:SV were significantly higher for the healthy older adults and the patients with VaMCI than for the patients with VD.

3.3. MMSE-2:EV

The MMSE-2:EV scores of the participants in the three groups are shown in Table 6. An ANCOVA that controlled for age, education, and gender revealed significant differences among the three groups on the MMSE-2:EV. Tukey' s *post hoc* analyses showed that the total score of the MMSE-2:EV was significantly higher for the healthy older adults than for the patients with VaMCI and the patients with VD, and it was also significantly higher for the patients with VaMCI than for the patients with VD. Particularly, among the items of the MMSE-2:EV, the scores of recall, attention and calculation, language, story memory, and processing speed were significantly higher for the healthy older

adults than for the patients with VaMCI and the patients with VD, and the scores of five items were also significantly higher for the patients with VaMCI than for the patients with VD. However, there were no significant differences in the items registration, orientation to time, orientation to place, and drawing between the healthy older adults and the patients with VaMCI, but the scores of four items on the MMSE-2:EV were significantly higher for the healthy older adults and the patients with VaMCI than for the patients with VD.

4. Reliability analyses

4.1. Internal Consistency

The internal reliability (Cronbach's α) of three versions of the MMSE-2 (red and blue forms) among the three groups are presented in Table 7. The internal reliability was relatively high because alphas ranged from 0.62 to 0.74.

4.2. Test-retest reliability

Eleven patients with VaMCI, 5 patients with VD, and 4 healthy older adults were tested twice, at an interval that averaged 31.35 ± 7.53 days, to examine the test-retest reliability. The mean age of the participants was 72.35 ± 7.13 years and the mean number of years of education was 11.60 ± 3.62 years. The test-retest reliability of three versions of the MMSE-2 was high, ranging from 0.62 to 0.99 (Table 8).

4.3. Interrater reliability

Two trained neuropsychologists were present during the administration of the MMSE-2 to 32 participants. One-way, single-measure intraclass correlation coefficients (ICCs) were calculated for each item of the MMSE-2 (Table 9). The ICCs ranged from 0.95 to 0.99. There was 100% agreement for orientation to place, naming, repetition, comprehension, reading, writing, and drawing.

5. Validity analyses

5.1. Concurrent validity

The concurrent validity of the MMSE-2 was examined through correlation with the values of the K-MMSE, the SVLT, the copy of RCFT, the SWF-animal, the PWF, the K-TMT-E: Part A & B, the DSC, and the K-BNT. The results showed that the three versions of the MMSE-2 were significantly correlated with the cognitive function tests (Table 10). Particularly, the correlation coefficients were high between the MMSE-2:BV and the MMSE ($r = 0.865$, $p < 0.01$), the MMSE-2:SV and the MMSE ($r = 0.947$, $p < 0.01$), and the MMSE-2:EV and the MMSE ($r = 0.839$, $p < 0.01$).

5.2. Discriminant validity by CDR stage analysis

To examine the utility of the MMSE-2 to detect dementia severity, the participants were reclassified into five groups according to their CDR and CDR-SOB scores. Specifically, the healthy older adults were assigned a CDR score of 0 (CDR-SOB 0), the patients with VaMCI were assigned a CDR score of 0.5 (CDR-SOB 0.5-2.5), the patients with early stage of VD were assigned a CDR score of 0.5 (CDR-SOB 3.0-4.0), the patients with mild stage of VD were assigned a CDR score of 1 (CDR-

SOB 4.5–9.0), and the patients with moderate stage of VD were assigned a CDR score of 2 (CDR–SOB 9.5–15.5). The average age, educational level, and gender of the participants are shown in Table 11. Although there was no significant difference in gender, $\chi^2(1,187) = 8.68$, $p = 0.70$, and education, $F(4,182) = 2.041$, $p = 0.90$, among the five groups, there were significant differences in age, $F(4,182) = 3.426$, $p < 0.01$.

The scores of all three versions of the MMSE–2 for the participants in the five groups are presented in Table 12. An ANCOVA that controlled for age revealed significant differences among the five groups in all three versions of the MMSE–2. According to Tukey's *post hoc* analyses, the five groups differed significantly with respect to the scores of the MMSE–2:BV and the MMSE–2:SV. However, on the MMSE–2:EV, the three groups (VaMCI, moderate stage of VD, and healthy older adults) differed significantly, but there was no significant difference between the patients with early stage of VD and the patients with mild stage of VD.

6. Diagnostic utility

To measure the diagnostic utility of the three versions of the MMSE-2, the ROC curve analysis and the area under the curve (AUC) was calculated. The results of each version of the MMSE-2 were as follows.

6.1. MMSE-2:BV

First, for discriminating the healthy older adults from the patients with VaMCI, the AUC of the MMSE-2:BV was 0.79 (95% confidence interval, CI, 0.71-0.86, $p < 0.001$). The sensitivity of the MMSE-2:BV was 84% and the specificity was 58% when using a cut-off score of ≤ 13 of 16 to predict VaMCI. Second, for discriminating the patients with VaMCI from the patients with VD, the AUC of the MMSE-2:BV was 0.89 (95% CI, 0.84-0.95, $p < 0.001$). The sensitivity of the MMSE-2:BV was 85% and the specificity was 72% when using a cut-off score of ≤ 11 of 16 to predict VD. Finally, for discriminating the healthy older adults from the patients with VD, the AUC of the MMSE-2:BV was 0.99 (95% CI, 0.97-1.00, $p < 0.001$). The sensitivity of the MMSE-2:BV was

100% and the specificity was 72% when using a cut-off score of ≤ 11 of 16 to predict VD (Figure 1).

6.2. MMSE-2:SV

First, for discriminating the healthy older adults from the patients with VaMCI, the AUC of the MMSE-2:SV was 0.87 (95% CI, 0.81-0.92, $p < 0.001$). The sensitivity of the MMSE-2:SV was 81% and the specificity was 80% when using a cut-off score of ≤ 26 of 30 to predict VaMCI. Second, for discriminating the patients with VaMCI from the patients with VD, the AUC of the MMSE-2:SV was 0.97 (95% CI, 0.94-0.99, $p < 0.001$). The sensitivity of the MMSE-2:SV was 82% and the specificity was 98% when using a cut-off score of ≤ 23 of 30 to predict VD. Finally, for discriminating the healthy older adults from the patients with VD, the AUC of the MMSE-2:SV was 0.99 (95% CI, 0.99-1.00, $p < 0.001$). The sensitivity of the MMSE-2:SV was 100% and the specificity was 98% when using a cut-off score of ≤ 23 of 30 to predict VD (Figure 2).

6.3. MMSE-2:EV

First, for discriminating the healthy older adults from the patients with VaMCI, the AUC of the MMSE-2:EV was 0.90 (95% CI, 0.85–0.95, $p < 0.001$). The sensitivity of the MMSE-2:EV was 83% and the specificity was 82% when using a cut-off score of ≤ 44 of 90 to predict VaMCI. Second, for discriminating the patients with VaMCI from the patients with VD, the AUC of the MMSE-2:EV was 0.94 (95% CI, 0.89–0.98, $p < 0.001$). The sensitivity of the MMSE-2:EV was 85% and the specificity was 85% when using a cut-off score of ≤ 33 of 90 to predict VD. Finally, for discriminating the healthy older adults from the patients with VD, the AUC of the MMSE-2:EV was 0.99 (95% CI, 0.99–1.00, $p < 0.001$). The sensitivity of the MMSE-2:EV was 100% and the specificity was 85% when using a cut-off score of ≤ 33 of 90 to predict VD (Figure 3).

Discussion

This study verified the newly developed MMSE-2 as a reliable and valid cognitive screening measure for the patients with VaMCI and VD in a Korean population. The results demonstrated several key points.

First, the results of the MMSE-2 and other neuropsychological assessments among the three groups (healthy older adults, VaMCI, and VD) which measure attention, verbal memory, visuospatial function, language function, and frontal/executive function were significantly differed.

Second, the MMSE-2 was shown to have good internal consistency, high test-retest reliability, and high inter-rater reliability.

Third, the MMSE-2 was also highly correlated with various neuropsychological assessments with verified validity. Particularly, the MMSE-2 had a very high correlation with the K-MMSE, and it also demonstrated a high correlation with verbal memory, visuospatial function, language function, and frontal lobe function tests. This result is consistent with the results in study 1. As mentioned before, even though there is executive function test in the MMSE such as attention

and calculation, the MMSE is insensitive to impairments in executive functioning, abstract reasoning, and visual perception/concentration (Nys et al., 2005). However, as Folstein et al. (2010) suggested that the MMSE-2 has shown its ability to measure executive function in more detail, and thus it can measure a greater variety of cognitive functions than the MMSE.

Fourth, as similar with the results in study 1, the scores of the MMSE-2 could also discriminate across each of the CDR and CDR-SOB stages. Therefore, the scores of the MMSE-2 declined significantly as CDR and CDR-SOB scores increased, which confirmed that the MMSE-2 was able to discriminate across the stages of CDR and CDR-SOB. This showed that the MMSE-2 is a useful instrument as a screening measure for detecting the progress of cognitive impairment. However, with the MMSE-2:EV, there was no significant difference between the patients with early stage of VD and the patients with mild stage of VD with similar to the results in study 1. There is possible reason for this finding is that the difficulty levels of story memory and processing speed tests may not enough to sensitive to discriminate between the

patients with early stage of VD and the patients with mild stage of VD. Thus, the MMSE-2:BV and MMSE-2:SV can be more effective than the MMSE-2:EV in assessing cognitive functions of the patients with early to mild stages of VD.

The sensitivity and specificity of the three versions of the MMSE-2 in discriminating between the healthy older adults and the patients with VaMCI were tested: for the MMSE-2:BV, the sensitivity was 84% and the specificity was 58% at the cut-off score of 13/14; for the MMSE-2:SV, the sensitivity was 81% and the specificity was 80% at the cut-off score of 26/27; and for the MMSE-2:EV, the sensitivity was 83% and the specificity was 82% at the cut-off score of 44/45. All three versions of the MMSE-2 could similarly discriminate between the two groups.

The sensitivity and specificity of the three versions of the MMSE-2 in discriminating between the patients with VaMCI and the patients with VD were tested: for the MMSE-2:BV, the sensitivity was 85% and the specificity was 72% at the cut-off score of 11/12; for the MMSE-2:SV, the sensitivity was 82%, and the specificity was 98% at the cut-off

score of 23/24; and for the MMSE-2:EV, the sensitivity was 85% and the specificity was 85% at the cut-off score of 33/34. All three versions of the MMSE-2 could similarly discriminate between the two groups.

Finally, the sensitivity and specificity of three versions of the MMSE-2 in discriminating between the healthy older adults and the patients with VD were tested: for the MMSE-2:BV, the sensitivity was 100% and the specificity was 72% at the cut-off score of 11/12; for the MMSE-2:SV, the sensitivity was 100%, and the specificity was 89% at the cut-off score of 22/23; and for the MMSE-2:EV, the sensitivity was 100% and the specificity was 85% at the cut-off score of 33/34. All three versions of the MMSE-2 could similarly discriminate between the two groups.

Overall, as same as the results in study 1, the MMSE-2 is a useful screening tool for discriminating between the patients with VaMCI and the patients with VD and between healthy older adults and the patients with VD. Moreover, it is also more sensitive to discriminate between the healthy older adults and the patients with vascular cognitive

impairment (VCI) than that of the groups between the healthy older adults and the patients with MCI or AD, and it also has more high sensitivity to discriminate between the healthy older adults and the patients with VaMCI (84%) than to discriminate between the healthy older adults and the patients with MCI (60%) although the specificity is relatively low (58%). Nevertheless, the MMSE-2 is slightly more sensitive in this area than the MMSE, which has sensitivity of 70.3% to discriminate the patients with VD from the healthy older adults at the cut-off score of 23/24 (Kang et al., 1997).

In summary, according to these results, as Folstein et al. (2010) suggested, the MMSE-2 can be used as a valid and reliable screening measure for assessing cognitive impairment of the patients with VCI in Korea. In addition, although it has low specificity to discriminate the patients with VaMCI from the healthy older adults, its ability to distinguish the patients with VaMCI from the healthy older adults may be as highly sensitive, and also it has more high sensitivity than that of the group (MCI and healthy older adults).

Table 1. Order of neuropsychological assessments

Order	List of neuropsychological assessments
1	MMSE-2 (red form or blue form)
2	SVLT-immediate recall
3	RCFT-copy
4	SGDS
5	K-TMT-E: Part A
6	K-TMT-E: Part B
7	SVLT-delayed recall
8	SVLT-recognition
9	SWF-animal
10	PWF-ㄱ/ㅇ/ㄴ
11	K-BNT
12	DSC
13	MMSE

Abbreviations: MMSE-2, Mini-Mental State Examination-2; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; SGDS, Short version of the Geriatric Depression Scale; K-TMT-E: Part A, Korean-Trail Making Test-Elderly' s version: Part A; K-TMT-E: Part B, Korean-Trail Making Test-Elderly' s version: Part B; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; K-BNT, Korean-Boston Naming Test; DSC, Digit Symbol Coding; MMSE, Korean version of the Mini-Mental State Examination.

Table 2. Characteristics of participants (M±SD)

	All participants (n=187)		
	Normal (n=75)	VaMCI (n=66)	VD (n=46)
Age (years)	68.59±7.10 [*]	71.97±7.67	72.59±7.35 [†]
Education (years)	12.49±4.03	11.06±3.91	10.61±3.62 [‡]
Male/Female	29/46	36/30	29/17 [¶]

Abbreviations: M, Mean; SD, Standard deviation; VaMCI, Vascular Mild Cognitive impairment; VD, Vascular dementia.

Note.

^{*} $p < 0.019$ for Normal vs. VaMCI.

[†] $p < 0.012$ for Normal vs. VD.

[‡] $p < 0.028$ for Normal vs. VD.

[¶] $p < 0.01$ for Normal vs. VD.

Table 3. The results of neuropsychological assessments in the groups of normal, VaMCI, and VD (M±SD)

Neuropsychological assessments	N(1)	VaMCI(2)	VD(3)	F	df	Post-hoc
MMSE	28.31±1.50	26.02±2.07	20.20±3.22	176.53*	2, 181	1>2>3
SVLT-immediate recall	21.03±3.93	14.98±3.54	11.22±3.51	78.53*	2, 181	1>2>3
SVLT-delayed recall	6.92±1.71	2.67±2.00	1.48±1.79	116.87*	2, 181	1>2>3
SVLT-recognition	21.31±1.63	18.74±2.55	16.61±3.19	38.66*	2, 181	1>2>3
RCFT-copy	33.69±1.86	28.62±4.05	20.09±9.58	78.17*	2, 179	1>2>3
K-TMT-E: Part A	18.92±6.34	31.79±13.89	72.30±67.44	32.98*	2, 181	1=2>3
K-TMT-E: Part B	35.16±23.05	89.70±62.78	207.76±94.14	102.77*	2, 180	1>2>3
SWF-animal	17.83±4.48	12.00±3.43	6.61±3.40	104.49*	2, 181	1>2>3
PWF-ㄱ, ㅁ, ㄴ	31.77±12.14	18.29±8.61	7.91±6.28	69.61*	2, 180	1>2>3
K-BNT	50.03±6.72	41.44±9.80	30.59±11.51	63.16*	2, 181	1>2>3
DSC	59.88±18.08	38.80±13.70	22.24±12.15	74.30*	2, 180	1>2>3
SGDS	3.39±3.72	2.95±3.17	4.33±4.07	1.83	2, 181	1=2=3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; MMSE, Korean version of the Mini-Mental State Examination; SVLT, Seoul Verbal Learning Test; RCFT, Rey Complex Figure Test; K-TMT-E: Part A, Korean-Trail Making Test-Elderly' s version: Part A; K-TMT-E: Part B, Korean-Trail Making Test-Elderly' s version: Part B; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; K-BNT, Korean version of Boston Naming Test; DSC, Digit Symbol Coding; SGDS, Short version of the Geriatric Depression Scale; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Vascular Dementia.

Note.

* $p < 0.001$.

Table 4. The results of the MMSE-2:BV in the groups of normal, VaMCI, and VD (M±SD)

MMSE-2:BV	N(1)	VaMCI(2)	VD(3)	F	df	η^2	Post-hoc
Registration	2.96±0.20	2.88±0.37	2.37±0.80	20.42*	2, 181	0.184	1=2>3
Orientation to time	4.84±0.40	4.67±0.62	3.11±1.46	58.42*	2, 181	0.392	1=2>3
Orientation to place	4.96±0.20	4.80±0.43	3.89±0.92	55.26*	2, 181	0.379	1=2>3
Recall	1.85±0.93	0.83±0.90	0.35±0.60	33.58*	2, 181	0.271	1>2>3
Total score	14.61±1.08	13.14±1.46	9.70±2.46	108.61*	2, 181	0.545	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Vascular Dementia.

Note.

* $p < 0.001$.

Table 5. The results of the MMSE-2:SV in the groups of normal, VaMCI, and VD (M±SD)

MMSE-2:SV	N(1)	VaMCI(2)	VD(3)	F	df	η^2	Post-hoc
Registration	2.96±0.20	2.88±0.37	2.37±0.80	20.42*	2, 181	0.184	1=2>3
Orientation to time	4.84±0.40	4.67±0.62	3.11±1.46	58.42*	2, 181	0.392	1=2>3
Orientation to place	4.96±0.20	4.80±0.43	3.89±0.92	55.26*	2, 181	0.379	1=2>3
Recall	1.85±0.93	0.83±0.90	0.35±0.60	33.58*	2, 181	0.271	1>2>3
Attention and Calculation	4.41±0.79	3.67±1.16	2.13±1.52	55.71*	2, 181	0.381	1>2>3
Language	7.87±0.34	7.36±0.82	6.48±1.28	31.75*	2, 181	0.260	1>2>3
Drawing	0.97±0.16	0.92±0.27	0.61±0.49	19.71*	2, 181	0.179	1=2>3
Total Score	27.91±1.56	25.11±1.88	18.91±3.55	199.79*	2, 181	0.688	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; MMSE-2:SV, Mini-Mental State Examination-2:Standard Version; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Vascular Dementia.

Note.

* $p < 0.001$.

Table 6. The results of the MMSE-2:EV in the groups of normal, VaMCI, and VD (M \pm SD)

MMSE-2:EV	N(1)	VaMCI(2)	VD(3)	F	df	η^2	Post-hoc
Registration	2.96 \pm 0.20	2.88 \pm 0.37	2.37 \pm 0.80	20.42*	2, 181	0.184	1=2>3
Orientation to time	4.84 \pm 0.40	4.67 \pm 0.62	3.11 \pm 1.46	58.42*	2, 181	0.392	1=2>3
Orientation to place	4.96 \pm 0.20	4.80 \pm 0.43	3.89 \pm 0.92	55.26*	2, 181	0.379	1=2>3
Recall	1.85 \pm 0.93	0.83 \pm 0.90	0.35 \pm 0.60	33.58*	2, 181	0.271	1>2>3
Attention and calculation	4.41 \pm 0.79	3.67 \pm 1.16	2.13 \pm 1.52	55.71*	2, 181	0.381	1>2>3
Language	7.87 \pm 0.34	7.36 \pm 0.82	6.48 \pm 1.28	31.75*	2, 181	0.260	1>2>3
Drawing	0.97 \pm 0.16	0.92 \pm 0.27	0.61 \pm 0.49	19.71*	2, 181	0.179	1=2>3
Story memory	9.77 \pm 3.51	4.71 \pm 2.20	2.91 \pm 1.95	78.25*	2, 181	0.464	1>2>3
Processing speed	14.35 \pm 4.35	9.94 \pm 3.69	5.67 \pm 2.86	61.11*	2, 181	0.403	1>2>3
Total Score	52.00 \pm 7.49	39.71 \pm 5.65	27.48 \pm 6.57	196.98*	2, 181	0.685	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; MMSE-2:EV, Mini-Mental State Examination-2:Expanded Version; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Vascular Dementia.

Note.

* $p < 0.001$.

Table 7. Internal consistency: MMSE-2:BV, MMSE-2:SV, and MMSE-2:EV (red and blue forms)

MMSE-2	Red form			Blue form		
	N(r)	VaMCI(r)	VD(r)	N(r)	VaMCI(r)	VD(r)
BV	0.656	0.667	0.694	0.625	0.670	0.744
SV	0.644	0.643	0.622	0.642	0.479	0.697
EV	0.662	0.657	0.689	0.670	0.624	0.720

Abbreviations: N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; MMSE-2, Mini-Mental State Examination-2; BV, Brief version; SV, Standard version; EV, Expanded version; r, Cronbach's α coefficient.

Table 8. Test-retest reliability of the MMSE-2

MMSE-2	r	<u>1st Test</u>		<u>2nd Test</u>	
		M	SD	M	SD
BV	0.62*	12.30	2.08	12.70	2.68
SV	0.93*	24.05	4.02	24.65	9.93
EV	0.99*	39.30	11.95	39.80	11.48

Abbreviations: M, Mean; SD, Standard deviation; MMSE-2, Mini-Mental State Examination-2; BV, Brief version; SV, Standard version; EV, Expanded version; r, Pearson's correlation coefficient.

Note.

* $p < 0.01$.

Table 9. Interrater reliability of the MMSE-2

MMSE-2	ICC	% agreement
Registration	0.95	
Orientation to time	0.99	
Orientation to place	–	100%
Recall	0.98	
Attention and calculation	0.98	
Naming	–	100%
Repetition	–	100%
Comprehension	–	100%
Reading	–	100%
Writing	–	100%
Drawing	–	100%
Story memory	0.96	
Processing speed	0.99	

Abbreviations: MMSE-2, Mini-Mental State Examination-2; ICC, Intraclass Correlation Coefficient.

Table 10. Correlation between the MMSE-2 and cognitive measures

	1	2	3	4	5	6	7	8	9	10	11	12	13
1.MMSE-2:BV	1												
2.MMSE-2:SV	0.896*	1											
3.MMSE-2:EV	0.799*	0.877*	1										
4.MMSE	0.865*	0.947*	0.839*	1									
5.SVLT-IR	0.619*	0.625*	0.739*	0.620*	1								
6.SVLT-DR	0.660*	0.614*	0.727*	0.610*	0.831*	1							
7.SVLT-R	0.639*	0.590*	0.644*	0.574*	0.684*	0.747*	1						
8.RCFT-Copy	0.643*	0.774*	0.740*	0.766*	0.575*	0.512*	0.496*	1					
9.SWF-Animal	0.639*	0.704*	0.783*	0.665*	0.691*	0.656*	0.524*	0.614*	1				
10.PWF-Total	0.570*	0.677*	0.797*	0.661*	0.656*	0.618*	0.490*	0.616*	0.735*	1			
11.DSC	0.644*	0.729*	0.899*	0.720*	0.616*	0.628*	0.539*	0.679*	0.665*	0.754*	1		
12.K-TMT-E:A	-0.590*	-0.678*	-0.617*	-0.666*	-0.420*	-0.378	-0.425*	-0.710*	-0.500*	-0.439*	-0.547*	1	
13.K-TMT-E:B	-0.680*	-0.773*	-0.755*	-0.793*	-0.528*	-0.513	-0.460*	-0.750*	-0.580*	-0.580*	-0.688*	0.607*	1
14.K-BNT	0.623*	0.678*	0.700*	0.681*	0.556	0.552	0.492*	0.564*	0.654*	0.584*	0.606*	-0.498*	-0.610*

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief version; SV, Standard version; EV, Expanded version; MMSE, Korean version of Mini-Mental State Examination; SVLT-IR, Seoul Verbal Learning Test-Immediate Recall; DR, Delayed Recall; R, Recognition; RCFT, Rey Complex Figure Test; SWF, Semantic Word Fluency; PWF, Phonemic Word Fluency; DSC, Digit Symbol Coding; K-TMT-E, Korean-Trail Making Test-Elderly's version; K-BNT, Korean version of Boston Naming Test.

Note.

* $p < 0.01$.

Table 11. Participants' average age, education, and gender classified by CDR & CDR-SOB stage (M \pm SD)

	N(75)	VaMCI(66)	EVD(21)	MiVD(21)	MoVD(4)
	CDR 0, CDR-SOB 0	CDR 0.5, CDR-SOB 0.5-2.5	CDR 0.5, CDR-SOB 3.0-4.0	CDR 1, CDR-SOB 4.5-9.0	CDR 2, CDR-SOB 9.5-15.5
Age	68.59 \pm 7.10	71.97 \pm 7.67*	73.19 \pm 7.53	73.05 \pm 6.56	67.00 \pm 9.97
Education	12.49 \pm 4.03	11.06 \pm 3.91	10.67 \pm 4.16	10.67 \pm 3.26	10.00 \pm 3.16
Male/Female	29/46	36/30	15/6	12/9	2/2

Abbreviations: CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; EVD, Early stage of Vascular Dementia; MiVD, Mild stage of Vascular Dementia; MoVD, Moderate stage of Vascular Dementia.

Note.

* $p < 0.05$ for Normal vs. VaMCI.

Table 12. The results of the three versions of the MMSE-2 according to CDR & CDR-SOB (M±SD)

MMSE-2	N(1) CDR 0, CDR-SOB 0	VaMCI(2) CDR 0.5, CDR-SOB 0.5-2.5	EVD(3) CDR 0.5, CDR-SOB 3.0-4.0	MiVD(4) CDR 1, CDR-SOB 4.5-9.0	MoVD(5) CDR 2, CDR-SOB 9.5-15.5	F	df	Post-hoc
BV	14.61±1.08	13.14±1.46	11.24±1.70	8.90±2.02	5.75±1.50	97.75*	4, 181	1>2>3>4>5
SV	27.91±1.56	25.11±1.88	20.24±2.76	18.76±3.21	12.75±2.50	139.72*	4, 181	1>2>3>4>5
EV	52.00±7.49	39.71±5.65	30.14±3.86	27.19±6.49	15.00±2.94	111.56*	4, 181	1>2>3>4>5

Abbreviations: CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating-Sum of Boxes; M, Mean; SD, Standard deviation; MMSE-2, Mini-Mental State Examination; BV, Brief Version; SV, Standard Version; EV, Expanded Version; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; EVD, Early stage of Vascular Dementia; MiVD, Mild stage of Vascular Dementia; MoVD, Moderate stage of Vascular Dementia; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Early stage of Vascular Dementia; 4, Mild Stage of Vascular Dementia; 5, Moderate stage of Vascular Dementia.

Note.

* $p < 0.01$.

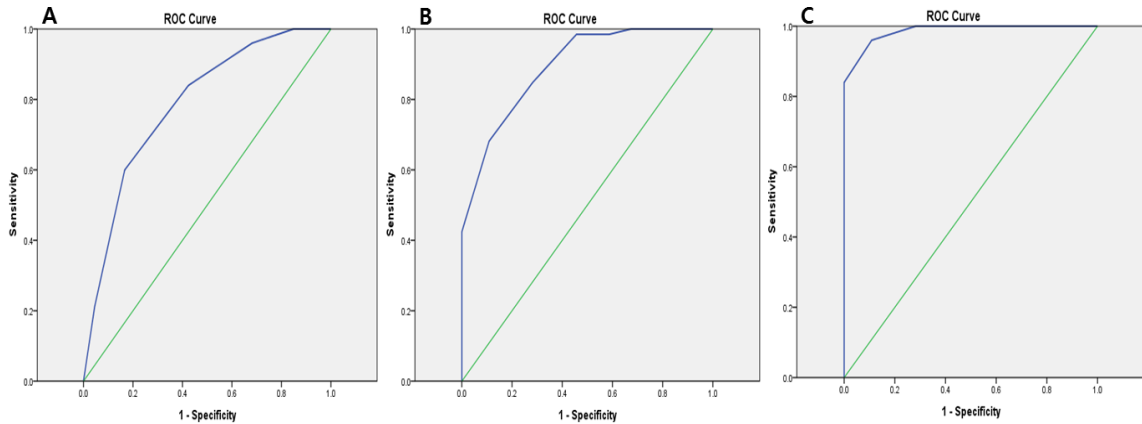


Figure 1. Mini-Mental State Examination-2: Brief Version (MMSE-2:BV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:BV in the groups of normal, vascular mild cognitive impairment (VaMCI), vascular dementia (VD). (A) Normal vs. VaMCI, Area Under the Curve (AUC)=0.79. (B) VaMCI vs. VD, Area Under the Curve (AUC)=0.89. (C) Normal vs. VD, Area Under the Curve (AUC)=0.99.

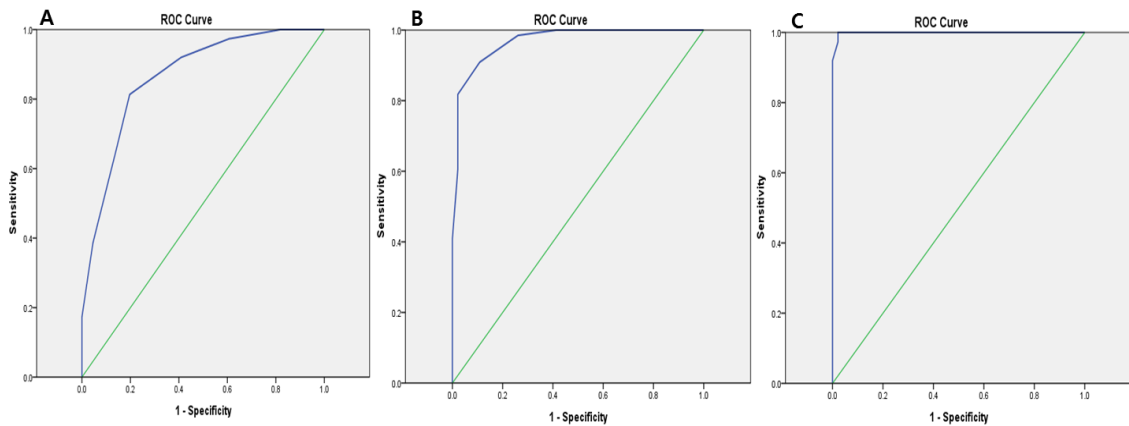


Figure 2. Mini-Mental State Examination-2:Standard Version (MMSE-2:SV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:SV in the groups of normal, vascular mild cognitive impairment (VaMCI), vascular dementia (VD). (A) Normal vs. VaMCI, Area Under the Curve (AUC)=0.87. (B) VaMCI vs. VD, Area Under the Curve (AUC)=0.97. (C) Normal vs. VD, Area Under the Curve (AUC)=0.99.

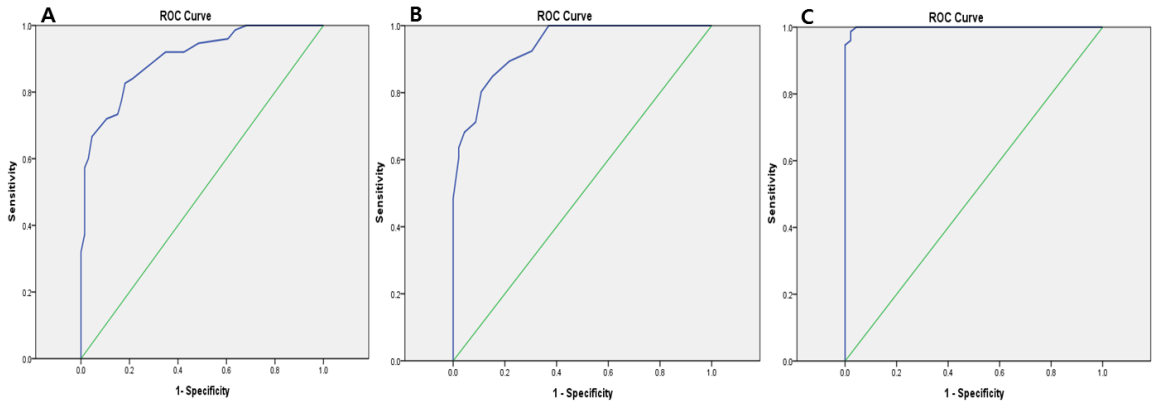


Figure 3. Mini-Mental State Examination-2:Expanded Version (MMSE-2:EV). Receiver operator characteristic (ROC) curve analysis of the MMSE-2:EV in the groups of normal, vascular mild cognitive impairment (VaMCI), and vascular dementia (VD). (A) Normal vs. VaMCI, Area Under the Curve (AUC)=0.90. (B) VaMCI vs. VD, Area Under the Curve (AUC)=0.94. (C) Normal vs. VD, Area Under the Curve (AUC)=0.99.

Study 5

Comparison between the Mini-Mental State Examination and the Mini-Mental State Examination-2 in Korean patients with Vascular Mild Cognitive Impairment and Vascular Dementia

Introduction

In study 4, the validity and reliability of the MMSE-2 in the patients with VaMCI and VD were verified, and also it showed that the MMSE-2 can be used clinically as a cognitive screening test to measure cognitive function of the patients with VCI.

Therefore, in study 5, the purpose of this study is to compare the usefulness of the MMSE-2 and the K-MMSE to determine which test is more sensitive in discriminating between normal cognitive aging and the patients with VaMCI and VD in a Korean population.

Materials and Methods

1. Participants

The groups of the patients (VaMCI and VD) and control participants were the same as study 4.

2. Instruments

2.1. MMSE-2

The description of the MMSE-2 was the same as that of study 1.

2.2. K-MMSE

The description of the K-MMSE was the same as that of study 2.

2.3. Other Neuropsychological Assessments

The MMSE-2 and the K-MMSE were performed with a time interval of at least 1 hour in order to compensate for the learning effect that could be occurred when using the MMSE-2 and the K-MMSE at the same time so the detailed neuropsychological assessments were

performed in the meantime. In the detailed neuropsychological assessments, there were SVLT (Kang et al., 2003) for assessing verbal memory, a copy of the RCFT (Meyers et al., 1995) for assessing visuospatial function, the SWF-Animal and the PWF (Kang et al., 2000), the Digit Symbol Coding (DSC) (Joy et al., 2004), and the Korean-Trail Making Test-Elderly's version: Part A & B (K-TMT-E) (Yi et al., 2007) for assessing executive function of the frontal lobe, the K-BNT (Kim et al., 1997) for assessing naming ability, the Short version of the Geriatric Depression Scale (SGDS) (Cho et al., 1999) for assessing depression. Moreover, global measurements, including CDR (Morris, 1993) & CDR-SOB (O'Bryant et al., 2008, 2010), were also conducted.

3. Procedure

The procedure of this study was the same as that of study 2.

4. Statistical Analysis

First, an ANOVA was used to compare age and educational levels, and a chi square test was used to compare gender across the three groups (66 patients with VaMCI, 46 patients with VD, and 75 healthy older adults). The results of the neuropsychological tests in the three groups were analyzed using an ANCOVA after controlling for demographic variables (age, education, and gender).

Second, the results of the MMSE-2 (BV, SV, and EV) in the three groups were analyzed using an ANCOVA after controlling for demographic variables (age, education, and gender) followed by Tukey's test for *post-hoc* analysis.

Third, the results of the K-MMSE in the three groups were analyzed using an ANCOVA after controlling for demographic variables (age, education, and gender) followed by Tukey's test for *post-hoc* analysis.

Fourth, the discrimination analysis was performed to examine the classification accuracy and discrimination of the patients with VaMCI and VD in the MMSE-2 and the K-MMSE.

Finally, to evaluate the sensitivity and specificity of the MMSE-2 and the K-MMSE for differentiating across the three groups were examined

using a receiver operating characteristic (ROC) curve and area under the curve (AUC) measurements.

Data were analyzed using IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered to be significant for all analyses.

Results

1. The demographic data of the participants

The demographic characteristics of the patients with VaMCI, the patients with VD, and the healthy older adults were the same as those of study 4.

2. The results of participants' neuropsychological assessments

The results of the neuropsychological assessments in the three groups (healthy older adults, VaMCI, and VD) were the same as those of study 4.

3. The results of the MMSE-2 in the groups of normal, VaMCI, and VD

3.1. MMSE-2:BV, SV, EV

The results of the MMSE-2 (BV, SV, and EV) in the three groups were the same as those of study 4.

4. The results of the K-MMSE in the groups of normal, VaMCI, and VD

The results of the K-MMSE scores in the three groups are presented in Table 1. An ANCOVA that controlled for age, education, and gender revealed significant differences across the three groups on the K-MMSE. According to Tukey's post hoc analyses, the scores of attention and calculation, recall, language, and total score of the K-MMSE were significantly higher for the healthy older adults than for the patients with VaMCI and VD, and they were significantly higher for the patients with VaMCI than for the patients with VD. However, there were no significant differences in the items such as orientation to time, orientation to place, and drawing between the healthy older adults and the patients with VaMCI, but the scores of three items in the K-MMSE were significantly higher for the two groups (healthy older adults and

VaMCI) than for the patients with VD. Moreover, there was no significant difference in the item, registration, across the three groups.

5. Comparison of the discriminant analysis between the MMSE-2 and the K-MMSE

5.1. MMSE-2

5.1.1. The discriminant analysis of the MMSE-2 in the groups of normal, VaMCI, and VD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the three groups (healthy older adults, VaMCI, and VD) as dependent variables. Two significant discriminant functions were calculated through analysis, and the results are presented in Table 2. The results showed the first function distinguished between the healthy older adults and the group of the patients (VaMCI and VD), and the second function distinguished between the patients with VaMCI and the patients with VD. The first function was statistically significant,

explained 88.6% of the total variance in the model (Wilk's Lambda = 0.188, $\chi^2 = 301.29$, $p < 0.001$), and the second function was also statistically significant, explained 11.4% of the total variance in the model (Wilk's Lambda = 0.729, $\chi^2 = 56.98$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest in the first function, and story memory was the most discriminating subtest in the second function (Table 3). Moreover, the structure matrix canonical loadings of the predictor variables and the two discriminant functions indicated that the first function was strongly correlated with processing speed (canonical loading = 0.531), attention and calculation (canonical loading = 0.466), orientation to place (canonical loading = 0.455), recall (canonical loading = 0.414), and language (canonical loading = 0.389). The second function was strongly correlated with story memory (canonical loading = -0.667) and orientation to time (canonical loading = 0.479) (Table 4). These results indicated that the best discriminative item between the healthy older adults and the group of the patients (VaMCI and VD) was

processing speed, and the best discriminative item between the patients with VaMCI and the patients with VD was story memory.

The results of classifying the samples by the two functions are presented in Table 5. According to the classification results, in the MMSE-2:BV, 75.8% of the patients with VaMCI, 67.4% of the patients with VD, and 62.7% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 68.4%. In the MMSE-2:SV, 75.8% of the patients with VaMCI, 76.1% of the patients with VD, and 72.0% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 74.3%. In the MMSE-2:EV, 81.8% of the patients with VaMCI, 80.4% of the patients with VD, and 78.7% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 80.2%.

5.1.2. The discriminant analysis of the MMSE-2 in the healthy older adults vs. the patients with VaMCI

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent variables and the two groups (healthy older adults and VaMCI) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 6. There was significant difference between the two groups over nine independent variables (Wilk's Lambda = 0.462, $\chi^2 = 103.79$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, story memory was the most discriminating subtest (Table 7). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with story memory (canonical loading = 0.794), recall (canonical loading = 0.519), processing speed (canonical loading = 0.506), language (canonical loading = 0.383), and attention and calculation (canonical loading = 0.356), but the function was not significantly correlated with orientation to place, orientation to time, registration, and drawing (Table 8). These results

indicated that the best discriminative item between the healthy older adults and the patients with VaMCI was story memory.

The results of classifying the samples by the function are presented Table 9. According to the classification results, in the MMSE-2:BV, 61.3% of the healthy older adults and 83.3% of the patients with VaMCI were correctly classified, and thus the overall classification accuracy was 71.6%. In the MMSE-2:SV, 76.0% of the healthy older adults and 80.3% of the patients with VaMCI were correctly classified, and thus the overall classification accuracy was 78.0%. In the MMSE-2:EV, 82.7% of the healthy older adults and 83.3% of the patients with VaMCI were correctly classified, and thus the overall classification accuracy was 83.0%.

5.1.3. The discriminant analysis of the MMSE-2 in the patients with VaMCI vs. the patients with VD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent

variables and the two groups (VaMCI and VD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 10. There was significant difference between the two groups over nine independent variables (Wilk's Lambda = 0.410, $\chi^2 = 94.16$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest (Table 11). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with orientation to time (canonical loading = 0.614), orientation to place (canonical loading = 0.554), processing speed (canonical loading = 0.522), attention and calculation (canonical loading = 0.484), registration (canonical loading = 0.359), language (canonical loading = 0.355), story memory (canonical loading = 0.354), and drawing (canonical loading = 0.347), but the function was not significantly correlated with recall (Table 12). These results indicated that the best discriminative item

between the patients with VaMCI and the patients with VD was orientation to time.

The results of classifying the samples by the function are presented Table 13. According to the classification results, in the MMSE-2:BV, 95.5% of the patients with VaMCI and 76.1% of the patients with VD were correctly classified, and thus the overall classification accuracy was 87.5%. In the MMSE-2:SV, 97.0% of the patients with VaMCI and 78.3% of the patients with VD were correctly classified, and thus the overall classification accuracy was 89.3%. In the MMSE-2:EV, 95.5% of the patients with VaMCI and 78.3% of the patients with VD were correctly classified, and thus the overall classification accuracy was 88.4%.

5.1.4. The discriminant analysis of the MMSE-2 in the healthy older adults vs. the patients with VD

The discriminant analysis by simultaneous input method was performed by using the nine subtests of the MMSE-2 as independent

variables and the two groups (healthy older adults and VD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 14. There was significant difference between the two groups over nine independent variables (Wilk's Lambda = 0.888, $\chi^2 = 178.18$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest (Table 15). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with story memory (canonical loading = 0.576), processing speed (canonical loading = 0.569), attention and calculation (canonical loading = 0.516), recall (canonical loading = 0.465), orientation to place (canonical loading = 0.459), orientation to time (canonical loading = 0.459), and language (canonical loading = 0.423), but the function was not significantly correlated with registration and drawing (Table 16). These results indicated that the best discriminative item between the healthy older adults and the patients with VD was story memory.

The results of classifying the samples by the function are presented Table 17. According to the classification results, in the MMSE-2:BV, 96.0% of the healthy older adults and 87.0% of the patients with VD were correctly classified, and thus the overall classification accuracy was 92.6%. In the MMSE-2:SV, 100.0% of the healthy older adults and 91.3% of the patients with VD were correctly classified, and thus the overall classification accuracy was 96.7%. In the MMSE-2:EV, 100.0% of the healthy older adults and 97.8% of the patients with VD were correctly classified, and thus the overall classification accuracy was 99.2%.

5.2. K-MMSE

5.2.1. The discriminant analysis of the K-MMSE in the groups of normal, VaMCI, and VD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the three groups (healthy older adults, VaMCI, and VD)

as dependent variables. Two significant discriminant functions were calculated through analysis, and the results are presented in Table 18. The results showed that the first function distinguished between the healthy older adults and the group of the patients (VaMCI and VD), and the second function distinguished between the patients with VaMCI and the patients with VD. The first function was statistically significant, explained 95.5% of the total variance in the model (Wilk's Lambda = 0.295, $\chi^2 = 220.85$, $p < 0.001$), and the second function was also statistically significant, explained 4.5% of the total variance in the model (Wilk's Lambda = 0.910, $\chi^2 = 17.07$, $p < 0.05$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, attention and calculation was the most discriminating subtest in the first function, and recall was the most discriminating subtest in the second function (Table 19). Moreover, the structure matrix canonical loadings of the predictor variables and the two discriminant functions indicated that the first function was strongly correlated with orientation to time (canonical loading = 0.577), orientation to place (canonical loading = 0.555),

attention and calculation (canonical loading = 0.546), language (canonical loading = 0.412), and drawing (canonical loading = 0.314). The second function was strongly correlated with recall (canonical loading = 0.538) and registration (canonical loading = 0.100) (Table 20). These results indicated that the best discriminative item between the healthy older adults and the group of the patients (VaMCI and VD) was orientation to time, and the best discriminative item between the patients with VaMCI and the patients with VD was recall.

The results of classifying the samples by the two functions are presented in Table 21. According to the classification results, 63.6% of the patients with VaMCI, 80.4% of the patients with VD, 72.0% of the healthy older adults were correctly classified, and thus the overall classification accuracy was 71.1%.

5.2.2. The discriminant analysis of the K-MMSE in the healthy older adults vs. the patients with VaMCI

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (healthy older adults and VaMCI) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 22. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.688, $\chi^2 = 50.65$, $p < 0.05$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, language was the most discriminating subtest (Table 23). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with attention and calculation (canonical loading = 0.571), language (canonical loading = 0.566), recall (canonical loading = 0.561), and orientation to place (canonical loading = 0.353), but the function was not significantly correlated with orientation to time, registration, and drawing (Table 24). These results indicated that the best discriminative item between the

healthy older adults and the patients with VaMCI was attention and calculation.

The results of classifying the samples by the function are presented in Table 25. According to the classification results, 84.0% of the healthy older adults and 84.0% of the patients with VaMCI was correctly classified, and thus the overall classification accuracy was 73.8%.

5.2.3. The discriminant analysis of the K-MMSE in the patients with VaMCI vs. the patients with VD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (VaMCI and VD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 26. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.447, $\chi^2 = 85.71$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, orientation to time was the most discriminating subtest (Table 27). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with orientation to time (canonical loading = 0.670), orientation to place (canonical loading = 0.598), attention and calculation (canonical loading = 0.519), drawing (canonical loading = 0.374), language (canonical loading = 0.340), and recall (canonical loading = 0.318), but the function was not significantly correlated with registration (Table 28). These results indicated that the best discriminative item between the patients with VaMCI and the patients with VD was orientation to time.

The results of classifying the samples by the function are presented in Table 29. According to the classification results, 89.4% of the patients with VaMCI and 80.4% of the patients with VD was correctly classified, and thus the overall classification accuracy was 85.7%.

5.2.4. The discriminant analysis of the healthy older adults vs. the patients with VD

The discriminant analysis by simultaneous input method was performed by using the seven subtests of the K-MMSE as independent variables and the two groups (healthy older adults and VD) as dependent variables. One significant discriminant function was calculated through analysis, and the results are presented in Table 30. There was significant difference between the two groups over seven independent variables (Wilk's Lambda = 0.247, $\chi^2 = 161.51$, $p < 0.001$).

According to the results of the standardized canonical discriminant function coefficients in the discriminant function, attention and calculation was the most discriminating subtest (Table 31). Moreover, the structure matrix canonical loadings of the predictor variables and the discriminant function indicated that the function was strongly correlated with attention and calculation (canonical loading = 0.564), orientation to place (canonical loading = 0.508), orientation to time (canonical loading = 0.508), language (canonical loading = 0.429), and recall (canonical loading = 0.426), but the function was not significantly

correlated with drawing and registration (Table 32). These results indicated that the best discriminative item between the healthy older adults and the patients with VD was attention and calculation.

The results of classifying the samples by the function are presented in Table 33. According to the classification results, 98.7% of the healthy older adults and 93.5% of the patients with VD was correctly classified, and thus the overall classification accuracy was 96.7%.

6. Diagnostic utility of the MMSE-2 and the K-MMSE

6.1. MMSE-2

The results of each version of the MMSE-2 (BV, SV, and EV) were the same as in the study 4.

6.2. K-MMSE

The ROC curve analysis and the area under the curve (AUC) was performed to verify the diagnostic utility of the K-MMSE in the patients with VaMCI, the patients with VD, and the healthy older adults.

First, for discriminating the healthy older adults from the patients with VaMCI, the AUC of the K-MMSE was 0.81, (95% CI, 0.74–0.88, $p < 0.001$). The sensitivity of the K-MMSE was 72% and the specificity was 76% when using a cut-off score ≤ 27 of 30 to predict VaMCI. Second, for discriminating the patients with VaMCI from the patients with VD, the AUC of the K-MMSE was 0.95, (95% CI, 0.91–0.99, $p < 0.001$). The sensitivity of the K-MMSE was 89% and the specificity was 85% when using a cut-off score ≤ 23 of 30 to predict VD. Finally, for discriminating the healthy older adults from the patients with VD, the AUC of the K-MMSE was 1.00 (95% CI, 0.99–1.00), $p < 0.001$. The sensitivity of the K-MMSE was 100% and the specificity was 85% when using a cut-off score ≤ 23 of 30 to predict VD (Figure 1).

7. Comparison between the MMSE-2 and the K-MMSE

7.1. Comparison between the healthy older adults and the patients with VaMCI

7.1.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults and the patients with VaMCI. The AUC of the MMSE-2:BV was 0.786, and the AUC of the K-MMSE was 0.809, but there was no significant difference between the two tests (Table 34).

7.1.2. The MMSE-2:SV vs. the K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults and the patients with VaMCI. The AUC of the MMSE-2:SV was 0.865, and the AUC of the K-MMSE was 0.809, and the AUC of the MMSE-2:SV was significantly higher than that of the K-MMSE (Table 34).

7.1.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in

discriminating between the healthy older adults and the patients with VaMCI. The AUC of the MMSE-2:EV was 0.902, and the AUC of the K-MMSE was 0.809, and the AUC of the MMSE-2:EV was significantly higher than that of the K-MMSE (Table 34).

7.2. Comparison between the patients with VaMCI and the patients with VD

7.2.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the patients with VaMCI and the patients with VD. The AUC of the MMSE-2:BV was 0.893, and the AUC of the K-MMSE was 0.949, and the AUC of the K-MMSE was significantly higher than that of the MMSE-2:BV (Table 35).

7.2.2. The MMSE-2:SV vs. K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in

discriminating between the patients with VaMCI and the patients with VD. The AUC of the MMSE-2:SV was 0.968, and the AUC of the K-MMSE was 0.949, but there was no significant difference between the two tests (Table 35).

7.2.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the patients with VaMCI and the patients with VD. The AUC of the MMSE-2:EV was 0.921, and the AUC of the K-MMSE was 0.949, but there was no significant difference between the two tests (Table 35).

7.3. Comparison between the healthy older adults and the patients with VD

7.3.1. The MMSE-2:BV vs. the K-MMSE

The MMSE-2:BV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in

discriminating between the healthy older adults and the patients with VD. The AUC of the MMSE-2:BV was 0.986, and the AUC of the K-MMSE was 0.997, but there was no significant difference between the two tests (Table 36).

7.3.2. The MMSE-2:SV vs. the K-MMSE

The MMSE-2:SV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults and the patients with VD. The AUC of the MMSE-2:SV was 0.999, and the AUC of the K-MMSE was 0.997, but there was no significant difference between the two tests (Table 36).

7.3.3. The MMSE-2:EV vs. the K-MMSE

The MMSE-2:EV and the K-MMSE were compared with the ROC curve analysis to determine which test was more sensitive in discriminating between the healthy older adults and the patients with VD. The AUC of the MMSE-2:EV was 0.999, and the AUC of the K-

MMSE was 0.997, but there was no significant difference between the two tests (Table 36).

Discussion

In study 5, the MMSE-2 and the K-MMSE were compared to determine which test is more sensitive in discriminating across the three groups (healthy older adults, VaMCI, and VD).

The main results of study 5 were as follows. First, the results of the MMSE-2 (BV, SV, and EV) and the K-MMSE were significantly differed across the three groups (healthy older adults, VaMCI, and VD). In all three versions of the MMSE-2 (BV, SV, and EV), the subtests in the MMSE-2 such as recall ($\eta^2 = 0.27$), attention and calculation ($\eta^2 = 0.38$), language ($\eta^2 = 0.26$), story memory ($\eta^2 = 0.46$), and processing speed ($\eta^2 = 0.40$) of the healthy older adults were significantly higher than those of the patients with VaMCI and VD, and also the items of the MMSE-2 of the patients with VaMCI were significantly higher than those of the patients with VD. In the patients with VaMCI and VD, deficits of executive function as well as verbal memory are most distinct from those of the patients with MCI and AD.

In addition, among the subtests of the K-MMSE, the subtests in the K-MMSE such as attention and calculation ($\eta^2 = 0.38$), recall ($\eta^2 =$

0.18), and language ($\eta^2 = 0.22$) of the healthy older adults were significantly higher than those of the patients with VaMCI and VD, and also the items of the K-MMSE of the patients with VaMCI were significantly higher than those of the patients with VD.

When comparing the magnitude of the recall test in the MMSE-2 ($\eta^2 = 0.27$) and the K-MMSE ($\eta^2 = 0.18$), the recall test of the MMSE-2 could be seen to discriminate each group slightly more sensitively than the K-MMSE. Moreover, when comparing the magnitude of the story memory test in the MMSE-2 ($\eta^2 = 0.46$) with the recall tests in the MMSE-2 ($\eta^2 = 0.27$) and the K-MMSE ($\eta^2 = 0.18$), among the verbal memory tests, the story memory test could discriminate each group more sensitively than the recall. Therefore, the verbal memory tests (story memory and recall) in the MMSE-2 might be more sensitive to discriminate across the three groups (healthy older adults, VaMCI, and VD) than those of the K-MMSE.

Second, in the MMSE-2, the magnitude of the subtests related with executive function, processing speed ($\eta^2 = 0.40$) and attention and calculation ($\eta^2 = 0.38$), were higher than those of the recall test

related with verbal memory ($\eta^2 = 0.27$) in the MMSE-2. Moreover, in the K-MMSE, the magnitude of the subtest related with executive function, attention and calculation ($\eta^2 = 0.38$), was higher than those of the recall test ($\eta^2 = 0.18$) related with verbal memory in the K-MMSE. According to these results, the executive function test is more sensitive than the verbal memory test to distinguish the patients with VaMCI and VD from the healthy older adults.

Third, the results of the discriminant analysis of the MMSE-2 were as follows. In the MMSE-2, the subtests which discriminated significantly between the healthy older adults and the group of patients (VaMCI and VD) were processing speed, attention and calculation, orientation to place, recall, language, registration, and drawing. Moreover, the subtests which discriminated significantly between the patients with VaMCI and the patients with VD were story memory and orientation to time. The processing speed and attention and calculation are the tests which measure psychomotor ability and working memory of the frontal lobe functions, and orientation to time, orientation to place, recall, and story memory are the tests that measure episodic memory. As shown in

many previous studies, these results suggested that tests related with the frontal lobe function are important variables in group discrimination because the frontal lobe function is one of the first deteriorating functions of the patients with VaMCI or the patients with VD (O'Brien et al., 2003; Erkinjuntti et al., 2000; Bombois et al., 2007). Moreover, when discriminating between the patients with VaMCI and the patients with VD, it was shown that the story memory and recall tests related with episodic memory are more sensitive than the tests related with the frontal lobe function so it is important to measure episodic memory as dementia progresses.

Fourth, in the MMSE-2, the subtests that discriminated significantly between the healthy older adults and the patients with VaMCI were story memory, recall, processing speed, language, and attention and calculation. Thus, these results also showed that measuring the frontal lobe and language functions rather than episodic memory are more sensitive to discriminate between the two groups (healthy older adults and VaMCI). This is the result of supporting the previous studies (Han et al., 2006; Xu et al., 2014; Dong et al., 2010). Moreover, as shown in

study 3, the story memory test can be considered as the most sensitive test because it measures not only the verbal memory but also the general brain function, especially the frontal lobe function.

Fifth, in the MMSE-2, the subtests that discriminated significantly between the patients with VaMCI and the patients with VD were orientation to time, orientation to place, processing speed, attention and calculation, recall, language, story memory, and drawing. These results showed that as the dementia progressed, orientation tests, one of the tests for measuring episodic memory, discriminated the two groups (VaMCI and VD) more sensitively than the tests related with the frontal lobe function, and the story memory test, which was a relatively difficult test, was not sensitive to discriminate between the two groups. This is the same result as in study 2.

Sixth, the results of the discriminant analysis of the K-MMSE were as follows. In the K-MMSE, the subtests that discriminated significantly between the healthy older adults and the group of patients (VaMCI and VD) were orientation to time, orientation to place, attention and calculation, language, and drawing. Moreover, the subtests that

discriminated significantly between the patients with VaMCI and the patients with VD were orientation to time, orientation to place, attention and calculation, drawing, language, and recall. Therefore, as the dementia progressed, orientation tests, one of the tests for measuring episodic memory, were the most sensitive to discriminate the two groups (VaMCI and VD). Therefore, in the K-MMSE, as in the MMSE-2, the tests related with the frontal lobe function were more sensitive to distinguish between the healthy older adults and the patients with VCI than those of measuring episodic memory, and also it showed that as the dementia progressed, the tests related with episodic memory were more sensitive than the tests related with the frontal lobe function.

Seventh, in the K-MMSE, the subtests that discriminated significantly between the healthy older adults and the patients with VD were attention and calculation, language, recall, and orientation to place. These results also showed that the tests related with the frontal lobe and language functions were the most sensitive to discriminate between the two groups (healthy older adults and VD). In conclusion, it is

important to evaluate the frontal lobe function when evaluating early stage of VCI in both MMSE-2 and the K-MMSE, and it has been shown that the test related with episodic memory is the most sensitive for group discrimination as the dementia progresses.

Comparing the results of the discriminant analysis of the MMSE-2 and the K-MMSE comprehensively, the classification accuracy of the MMSE-2 in the three groups was 80.2%, and the classification accuracy of the K-MMSE in the three groups was 71.1%, suggesting that the MMSE-2 was more accurate than the K-MMSE. In more detail, the accuracy rate of classifying the healthy older adults and the patients with VaMCI was 83.0% for the MMSE-2 and 73.8% for the K-MMSE, suggesting that the MMSE-2 was more sensitive and accurate than the K-MMSE. Moreover, the accuracy of classification of the patients with VaMCI and the patients with VD was 88.4% for the MMSE-2 and 85.7% for the K-MMSE, suggesting that the MMSE-2 was slightly more sensitive than K-MMSE to discriminate between the two groups. Finally, the accuracy of classification of the healthy older adults and the patients with VD was 99.2% for the MMSE-2 and 96.7% for the K-

MMSE, suggesting that the MMSE-2 was slightly more sensitive than K-MMSE to discriminate between the two groups. In summary, the MMSE-2 was a more sensitive test than the K-MMSE when discriminating across the three groups. Especially, the MMSE-2 was about 10% more accurate than the K-MMSE when discriminating between the healthy older adults and the patients with VaMCI. This result is similar to study 2. Moreover, even though there was no significant difference in discriminating between the patients with VaMCI and the patients with VD or between the healthy older adults and the patients with VD, the MMSE-2 was slightly more sensitive than the K-MMSE.

Finally, when the AUC of the MMSE-2 and the K-MMSE was compared, the MMSE-2:SV and MMSE-2:EV were more sensitive than the K-MMSE when discriminating between the healthy older adults and the patients with VaMCI, but even though there was no significant difference in the MMSE-2:BV and the K-MMSE when discriminating between the two groups (healthy older adults and VaMCI), the K-MMSE might seem to discriminate slightly more than the MMSE-2:BV. In other words, the reason for this result is that in the MMSE-2:BV, there is no

test for measuring the frontal lobe function than the K-MMSE. However, as in study 2, the MMSE-2:BV and the K-MMSE might seem to discriminate slightly more than the MMSE-2:SV and the MMSE-2:EV when discriminating the patients with VD from the healthy older adults or the patients with VaMCI. In other words, when discriminating the healthy older adults and the patients with VaMCI, the more difficult test and the tests related with the frontal lobe function are more sensitive to distinguish the groups, and when discriminating the patients with VD from the healthy older adults or the patients with VaMCI, it is found that a test with low difficulty is more sensitive for discrimination.

As in the study 2, the overall results showed that when discriminating between the healthy older adults and the group of the patients with VCI (VaMCI and VD), the MMSE-2:SV and the MMSE-2:EV are more sensitive and accurate to detect early cognitive decline than the K-MMSE or the MMSE-2:BV, but as the dementia progresses, the K-MMSE or the MMSE-2:BV may be more useful than the MMSE-2:SV and the MMSE-2:EV. Therefore, the MMSE-2 can be useful as a cognitive screening test for measuring cognitive function of patients in

clinical settings not only for the patients with AD but also for the patients with VCI.

Table 1. The results of the K-MMSE in the groups of normal, VaMCI, and VD (M \pm SD)

K-MMSE	N(1)	VaMCI(2)	VD(3)	F	df	η^2	Post-hoc
Orientation to time	4.84 \pm 0.40	4.68 \pm 0.61	3.11 \pm 1.46	59.30*	2, 181	0.40	1=2>3
Orientation to place	4.96 \pm 0.20	4.80 \pm 0.44	3.89 \pm 0.92	55.92*	2, 181	0.38	1=2>3
Registration	3.00 \pm 0.00	2.97 \pm 0.25	2.93 \pm 0.25	1.12	2, 181	0.01	1=2=3
Attention and Calculation	4.40 \pm 0.81	3.65 \pm 1.14	2.13 \pm 1.51	55.11*	2, 181	0.38	1>2>3
Recall	2.28 \pm 0.92	1.56 \pm 0.99	0.87 \pm 0.93	19.77*	2, 181	0.18	1>2>3
Language	7.87 \pm 0.34	7.41 \pm 0.80	6.65 \pm 1.22	25.75*	2, 181	0.22	1>2>3
Drawing	0.96 \pm 0.20	0.92 \pm 0.27	0.61 \pm 0.49	17.95*	2, 181	0.17	1=2>3
Total	28.31 \pm 1.50	26.02 \pm 2.07	20.20 \pm 3.22	176.53*	2, 181	0.66	1>2>3

Abbreviations: M, Mean; SD, Standard deviation; N, Normal; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; K-MMSE, Korean version of the Mini-Mental State Examination; 1, Normal; 2, Vascular Mild Cognitive Impairment; 3, Vascular Dementia.

Note.

* $p < 0.001$.

Table 2. The results by the discriminant analysis in the groups of normal, VaMCI, and VD (MMSE-2)

Function(s)	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	2.886	88.6	88.6	0.862	0.188	301.292	18	0.000
2	0.372	11.4	100.0	0.521	0.729	56.978	8	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 3. The standardized canonical discriminant function coefficients in the groups of normal, VaMCI, and VD (MMSE-2)

	Functions	
	1	2
Registration	0.055	0.234
Orientation to time	0.445	0.489
Orientation to place	0.163	0.278
Recall	0.239	-0.274
Attention and calculation	0.279	0.081
Language	0.426	0.092
Drawing	0.096	0.136
Story memory	0.377	-0.634
Processing speed	0.116	-0.095

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 4. The results of the structure matrix in the groups of normal, VaMCI, and VD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions	
	Function 1	Function 2
Processing speed	0.531*	-0.197
Attention and calculation	0.466*	0.114
Orientation to place	0.455*	0.393
Recall	0.414*	-0.390
Language	0.389*	0.048
Registration	0.289*	0.259
Drawing	0.272*	0.246
Story memory	0.583	-0.667*
Orientation to time	0.468	0.479*

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 5. Classification rates (%) by discriminant analysis in the groups of normal, VaMCI, and VD (MMSE-2)

MMSE-2		Predictive groups				
		Groups	Normal	VaMCI	VD	Total
BV	Frequency	Normal	47	28	0	75
		VaMCI	14	50	2	66
		VD	0	15	31	46
	%	Normal	62.7	37.3	0.0	100.0
		VaMCI	21.2	75.8	3.0	100.0
		VD	0.0	32.6	67.4	100.0
MMSE-2:BV Classification accuracy						68.4%
		Predictive groups				
		Groups	Normal	VaMCI	VD	Total
SV	Frequency	Normal	54	21	0	75
		VaMCI	12	50	4	66
		VD	1	10	35	46
	%	Normal	72.0	28.0	0.0	100.0
		VaMCI	18.2	75.8	6.1	100.0
		VD	2.2	21.7	76.1	100.0
MMSE-2:SV Classification accuracy						74.3%
		Predictive groups				
		Groups	Normal	VaMCI	VD	Total
EV	Frequency	Normal	59	16	0	75
		VaMCI	8	54	4	66
		VD	0	9	37	46
	%	Normal	78.7	21.3	0.0	100.0
		VaMCI	12.1	81.8	6.1	100.0
		VD	0.0	19.6	80.4	100.0
MMSE-2:EV Classification accuracy						80.2%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Table 6. The result by the discriminant analysis in the healthy older adults and the patients with VaMCI (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	1.163	100.0	100.0	0.733	0.462	103.793	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 7. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with VaMCI (MMSE-2)

	Function 1
Registration	-0.023
Orientation to time	0.186
Orientation to place	0.036
Recall	0.384
Attention and calculation	0.214
Language	0.472
Drawing	0.039
Story memory	0.595
Processing speed	0.064

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 8. The results of the structure matrix in the healthy older adults and the patients with VaMCI (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Story memory	0.794
Recall	0.519
Processing speed	0.506
Language	0.383
Attention and calculation	0.356
Orientation to place	0.220
Orientation to time	0.157
Registration	0.129
Drawing	0.105

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 9. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with VaMCI (MMSE-2)

MMSE-2		Predictive groups			
		Groups	Normal	VaMCI	Total
BV	Frequency	Normal	46	29	75
		VaMCI	11	55	66
	%	Normal	61.3	38.7	100.0
		VaMCI	16.7	83.3	100.0
	MMSE-2:BV Classification accuracy				71.6%
		Predictive groups			
		Groups	Normal	VaMCI	Total
SV	Frequency	Normal	57	18	75
		VaMCI	13	53	66
	%	Normal	76.0	24.0	100.0
		VaMCI	19.7	80.3	100.0
	MMSE-2:SV Classification accuracy				78.0%
		Predictive groups			
		Groups	Normal	VaMCI	Total
EV	Frequency	Normal	62	13	75
		VaMCI	11	55	66
	%	Normal	82.7	17.3	100.0
		VaMCI	16.7	83.3	100.0
	MMSE-2:EV Classification accuracy				83.0%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; VaMCI, Vascular Mild Cognitive Impairment.

Table 10. The result by the discriminant analysis in the patients with VaMCI and the patients with VD (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	1.441	100.0	100.0	0.768	0.410	94.155	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 11. The standardized canonical discriminant function coefficients in the patients with VaMCI and the patients with VD (MMSE-2)

	Function
	1
Registration	0.112
Orientation to time	0.563
Orientation to place	0.212
Recall	0.179
Attention and calculation	0.284
Language	0.420
Drawing	0.107
Story memory	0.132
Processing speed	0.155

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 12. The results of the structure matrix in the patients with VaMCI and the patients with VD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Orientation to time	0.614
Orientation to place	0.554
Processing speed	0.522
Attention and calculation	0.484
Registration	0.359
Language	0.355
Story memory	0.354
Drawing	0.347
Recall	0.252

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 13. Classification rates (%) by discriminant analysis in the patients with VaMCI and the patients with VD (MMSE-2)

MMSE-2		Predictive groups			
		Groups	VaMCI	VD	Total
BV	Frequency	VaMCI	63	3	66
		VD	11	35	46
	%	VaMCI	95.5	4.5	100.0
		VD	23.9	76.1	100.0
	MMSE-2:BV Classification accuracy				87.5%
		Predictive groups			
		Groups	VaMCI	VD	Total
SV	Frequency	VaMCI	64	2	66
		VD	10	36	46
	%	VaMCI	97.0	3.0	100.0
		VD	21.7	78.3	100.0
	MMSE-2:SV Classification accuracy				89.3%
		Predictive groups			
		Groups	VaMCI	VD	Total
EV	Frequency	VaMCI	63	3	66
		VD	10	36	46
	%	VaMCI	95.5	4.5	100.0
		VD	21.7	78.3	100.0
	MMSE-2:EV Classification accuracy				88.4%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Table 14. The result by the discriminant analysis in the healthy older adults and the patients with VD (MMSE-2)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	3.741	100.0	100.0	0.888	0.211	178.178	9	0.000

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VD, Vascular Dementia; 1, Normal vs. VD.

Table 15. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with VD (MMSE-2)

	Function
	1
Registration	0.038
Orientation to time	0.444
Orientation to place	0.152
Recall	0.206
Attention and calculation	0.320
Language	0.393
Drawing	0.048
Story memory	0.374
Processing speed	0.105

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VD, Vascular Dementia; 1, Normal vs. VD.

Table 16. The results of the structure matrix in the healthy older adults and the patients with VD (MMSE-2)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Story memory	0.576
Processing speed	0.569
Attention and calculation	0.516
Recall	0.465
Orientation to place	0.459
Orientation to time	0.459
Language	0.423
Registration	0.290
Drawing	0.280

Abbreviations: MMSE-2, Mini-Mental State Examination-2; VD, Vascular Dementia; 1, Normal vs. VD.

Table 17. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with VD (MMSE-2)

MMSE-2		Predictive groups			
		Groups	Normal	VD	Total
BV	Frequency	Normal	72	3	75
		VD	6	40	46
	%	Normal	96.0	4.0	100.0
		VD	13.0	87.0	100.0
	MMSE-2:BV Classification accuracy				92.6%
		Predictive groups			
		Groups	Normal	VD	Total
SV	Frequency	Normal	75	0	75
		VD	4	42	46
	%	Normal	100.0	0.0	100.0
		VD	8.7	91.3	100.0
	MMSE-2:SV Classification accuracy				96.7%
		Predictive groups			
		Groups	Normal	VD	Total
EV	Frequency	Normal	75	0	75
		VD	1	45	46
	%	Normal	100.0	0.0	100.0
		VD	2.2	97.8	100.0
	MMSE-2:EV Classification accuracy				99.2%

Abbreviations: MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; VD, Vascular Dementia.

Table 18. The result by the discriminant analysis in the groups of normal, VaMCI, and VD (K-MMSE)

Function(s)	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	2.083	95.5	95.5	0.822	0.295	220.845	14	0.000
2	0.099	4.5	100.0	0.300	0.910	17.073	6	0.009

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI; Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 19. The standardized canonical discriminant function coefficients in the groups of normal, VaMCI, and VD (K-MMSE)

	Functions	
	1	2
Orientation to time	0.148	-0.498
Orientation to place	0.282	-0.396
Registration	0.013	0.184
Attention and calculation	0.448	0.235
Recall	0.387	0.710
Language	0.378	0.337
Drawing	0.155	-0.178

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI; Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 20. The results of the structure matrix in the groups of normal, VaMCI, and VD (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions	
	Function 1	Function 2
Orientation to time	0.577*	-0.556
Orientation to place	0.555*	-0.373
Attention and calculation	0.546*	0.179
Language	0.412*	0.244
Drawing	0.314*	-0.285
Recall	0.392	0.538*
Registration	0.091	0.100*

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI; Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, Normal vs. VaMCI & VD; 2, VaMCI vs. VD.

Table 21. Classification rates (%) by discriminant analysis in the groups of normal, VaMCI, and VD (K-MMSE)

		Predictive groups			Total
	Groups	Normal	VaMCI	VD	
Frequency	Normal	54	21	0	75
	VaMCI	18	42	6	66
	VD	0	9	37	46
%	Normal	72.0	28.0	0.0	100.0
	VaMCI	27.3	63.6	9.1	100.0
	VD	0.0	19.6	80.4	100.0
Classification accuracy					71.1%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Table 22. The result by the discriminant analysis in the healthy older adults and the patients with VaMCI (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	0.453	100.0	100.0	0.558	0.688	50.646	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 23. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with VaMCI (K-MMSE)

	Function
	1
Orientation to time	0.205
Orientation to place	0.133
Registration	0.133
Attention and calculation	0.444
Recall	0.531
Language	0.555
Drawing	0.192

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 24. The results of the structure matrix in the healthy older adults and the patients with VaMCI (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Attention and calculation	0.571
Language	0.566
Recall	0.561
Orientation to place	0.353
Orientation to time	0.231
Registration	0.134
Drawing	0.115

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; 1, Normal vs. VaMCI.

Table 25. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with VaMCI (K-MMSE)

		Predictive groups		
	Groups	Normal	VaMCI	Total
Frequency	Normal	63	12	75
	VaMCI	25	41	66
%	Normal	84.0	16.0	100.0
	VaMCI	37.9	62.1	100.0
Classification accuracy				73.8%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment.

Table 26. The result by the discriminant analysis in the patients with VaMCI and the patients with VD (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	1.236	100.0	100.0	0.744	0.447	85.708	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 27. The standardized canonical discriminant function coefficients in the patients with VaMCI and the patients with VD (K-MMSE)

	Function
	1
Orientation to time	0.490
Orientation to place	0.307
Registration	0.003
Attention and calculation	0.445
Recall	0.313
Language	0.288
Drawing	0.158

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 28. The results of the structure matrix in the patients with VaMCI and the patients with VD (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Orientation to time	0.670
Orientation to place	0.598
Attention and calculation	0.519
Drawing	0.374
Language	0.340
Recall	0.318
Registration	0.063

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia; 1, VaMCI vs. VD.

Table 29. Classification rates (%) by discriminant analysis in the patients with VaMCI and the patients with VD (K-MMSE)

		Predictive groups		
	Groups	VaMCI	VD	Total
Frequency	VaMCI	59	7	66
	VD	9	37	46
%	VaMCI	89.4	10.6	100.0
	VD	19.6	80.4	100.0
Classification accuracy				85.7%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Table 30. The result by the discriminant analysis in the healthy older adults and the patients with VD (K-MMSE)

Function	Eigenvalue	% of variance	Cumulative %	Canonical Correlation	Wilk's Lambda	Chi-Square	df	p
1	3.049	100.0	100.0	0.868	0.247	161.514	7	0.000

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VD, Vascular Dementia; 1, Normal vs. VD.

Table 31. The standardized canonical discriminant function coefficients in the healthy older adults and the patients with VD (K-MMSE)

	Function
	1
Orientation to time	0.341
Orientation to place	0.234
Registration	-0.051
Attention and calculation	0.518
Recall	0.492
Language	0.441
Drawing	0.077

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VD, Vascular Dementia; 1, Normal vs. VD.

Table 32. The results of the structure matrix in the healthy older adults and the patients with VD (K-MMSE)

Discriminatory factors	Correlation with the discriminant functions
	Function 1
Attention and calculation	0.564
Orientation to place	0.508
Orientation to time	0.508
Language	0.429
Recall	0.426
Drawing	0.289
Registration	0.119

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VD, Vascular Dementia; 1, Normal vs. VD.

Table 33. Classification rates (%) by discriminant analysis in the healthy older adults and the patients with VD (K-MMSE)

		Predictive groups		
	Groups	Normal	VD	Total
Frequency	Normal	74	1	75
	VD	3	43	46
%	Normal	98.7	1.3	100.0
	VD	6.5	93.5	100.0
Classification accuracy				96.7%

Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; VD, Vascular Dementia.

Table 34. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the healthy older adults compared with the patients with VaMCI

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV*	13/14	0.786 [0.709, 0.851]	84%	58%
MMSE-2:SV [†]	26/27	0.865 [0.797, 0.917]	81%	80%
MMSE-2:EV [‡]	44/45	0.902 [0.841, 0.946]	83%	82%
K-MMSE	27/28	0.809 [0.734, 0.870]	72%	76%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examination-2: Brief Version; MMSE-2:SV, MMSE-2:Standard Version; MMSE-2:EV, MMSE-2:Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment.

Note.

* $p = 0.539$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.018$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.005$ for MMSE-2:EV vs. K-MMSE.

Table 35. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the patients with VaMCI compared with the patients with VD

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV*	11/12	0.893 [0.821, 0.944]	85%	72%
MMSE-2:SV [†]	23/24	0.968 [0.917, 0.992]	82%	98%
MMSE-2:EV [‡]	33/34	0.921 [0.876, 0.982]	85%	85%
K-MMSE	23/24	0.949 [0.891, 0.982]	89%	85%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examinaion-2: Brief Version; MMSE-2:SV, MMSE-2:Standard Version; MMSE-2:EV, MMSE-2:Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Note.

* $p = 0.029$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.186$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.571$ for MMSE-2:EV vs. K-MMSE.

Table 36. The AUC of the MMSE-2:BV, the MMSE-2:SV, the MMSE-2:EV, and the K-MMSE for the healthy older adults compared with the patients with VD

Tests	Cutoff	AUC [95% CI]	Sensitivity	Specificity
MMSE-2:BV*	11/12	0.986 [0.945, 0.999]	100%	72%
MMSE-2:SV [†]	23/24	0.999 [0.968, 1.000]	100%	98%
MMSE-2:EV [‡]	33/34	0.999 [0.968, 1.000]	100%	85%
K-MMSE	23/24	0.997 [0.963, 1.000]	100%	85%

Abbreviations: AUC, Area Under the Curve; MMSE-2:BV, Mini-Mental State Examinaion-2: Brief Version; MMSE-2:SV, MMSE-2:Standard Version; MMSE-2:EV, MMSE-2:Expanded Version; K-MMSE, Korean version of the Mini-Mental State Examination; VD, Vascular Dementia.

Note.

* $p = 0.071$ for MMSE-2:BV vs. K-MMSE.

[†] $p = 0.293$ for MMSE-2:SV vs. K-MMSE.

[‡] $p = 0.347$ for MMSE-2:EV vs. K-MMSE.

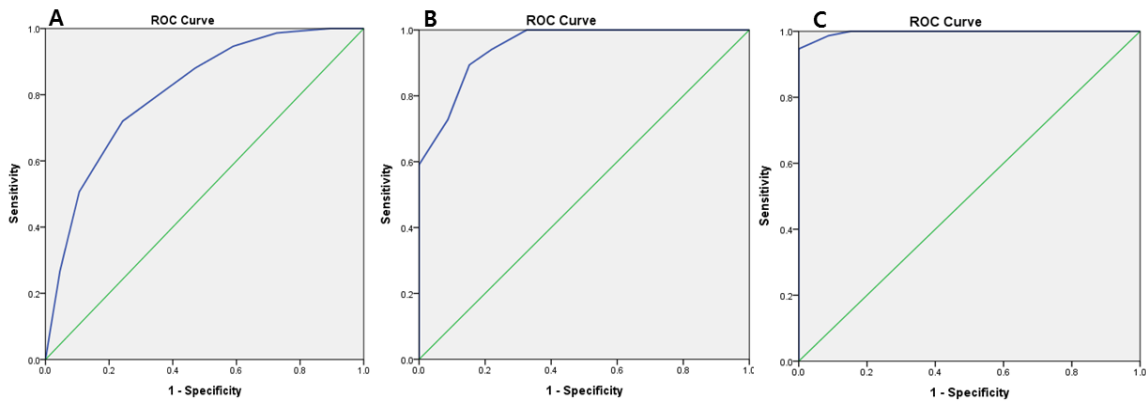


Figure 1. Korean version of the Mini-Mental State Examination (K-MMSE). Receiver operator characteristic (ROC) curve analysis of the K-MMSE in the groups of normal, vascular mild cognitive impairment (VaMCI), and vascular dementia (VD). (A) Normal vs. VaMCI, Area Under the Curve (AUC)=0.81. (B) VaMCI vs. VD, Area Under the Curve (AUC)=0.95. (C) Normal vs. VD, Area Under the Curve (AUC)=0.99.

Overall Discussion

In this study, the newly developed cognitive screening test, the MMSE-2 (Folstein et al., 2010), was translated into Korean to measure the reliability and validity of the MMSE-2, and then it was investigated whether the MMSE-2 can be used clinically as a diagnostic test for the patients with dementia in Korea. In the MMSE-2, the disadvantages of the MMSE (Folstein et al., 1975), which has been widely used as a cognitive screening test, was revised, and the story memory test which can assess verbal memory in detail and the processing speed test related with executive function of the frontal lobe were included. Therefore, it was investigated whether the MMSE-2 is reliable in distinguishing between the healthy older adults and the patients with dementia.

In this study, the five studies can be summarized into three major perspectives. First, according to the results in study 1 & 4, the validity and reliability of the MMSE-2 was examined for assessing patients with MCI, AD, VaMCI, and VD in a Korean population. The results are

summarized in Table 1. The MMSE-2 is useful for discriminating between the patients with MCI and the patients with AD, but its ability to discriminate between the healthy older adults and the patients with MCI is less than satisfactory. Moreover, in study 4, the MMSE-2 also can be used as a valid and reliable screening measure for assessing cognitive impairment to discriminate between the healthy older adults and the patients with VCI (VaMCI and VD). Although it had low specificity to discriminate the patients with MCI from the healthy older adults, its ability to distinguish the patients with VaMCI from the healthy older adults might be as highly sensitive, and also it had more high sensitivity than that of the groups (MCI and healthy older adults).

Second, in study 2 & 5, the usefulness of the MMSE-2 and the K-MMSE were compared to determine which test is more sensitive in discriminating between normal cognitive aging vs. the patients with MCI and AD and between normal cognitive aging vs. the patients with VaMCI and VD in a Korean population. Overall, the results showed that the MMSE-2:SV and the MMSE-2:EV were more sensitive and accurate to detect early cognitive decline of the patients with MCI or VaMCI

than that of the K-MMSE and the MMSE-2:BV. As the dementia (AD and VD) progressed, the K-MMSE and the MMSE-2:BV might be more useful than that of the MMSE-2:SV and the MMSE-2:EV. Therefore, the MMSE-2 is found to be more useful in the clinical setting as a cognitive screening test depending on the group of patients (Figure 1).

Finally, in study 3, the correlations between the total scores of the MMSE-2 and the K-MMSE with global volume changes in cortical gray matter measured by structural magnetic resonance imaging (MRI) using voxel-based morphometry (VBM) were examined, and also it was measured how they changed with progression of dementia. The results showed that the MMSE-2 was found to be more correlated with the atrophy of overall brain area than the K-MMSE. Especially, in the MMSE-2:EV, it had the highest correlation with the general brain area, and also the frontal lobe function could be measured which could not be measured by the K-MMSE (Figure 2).

Based on the above results, the findings and implications of this study are as follows.

First, in this study, it is significant that the MMSE-2 developed in 2010 is converted into Korean for the first time and the discrimination power of this test is evaluated in a Korean population. In addition, the reliability and validity of the MMSE-2 are measured in the various group of patients (MCI, AD, VaMCI, and VD), and it is confirmed that there is a difference in the discrimination power of the MMSE-2 according to the groups of patients. According to the results of the previous studies, unlike the MMSE, the MMSE-2 has a high reliability and validity in distinguishing between the patients with AD or the patients with VD from the healthy older adults. In particular, although not as high as expected, the MMSE-2 is somewhat sensitive to distinguish the patients with MCI or the patients with VaMCI from normal cognitive aging and proved to be more useful than the MMSE in clinical settings.

Second, it is also meaningful to compare the K-MMSE, which has been widely used in Korea as a cognitive screening test, and the newly developed MMSE-2 to evaluate which test is more useful in clinical settings. Considering the results of this study, as for the development

purpose of the MMSE-2, the MMSE-2:SV and the MMSE-2:EV are more sensitive and accurate to detect early cognitive decline of patients than the K-MMSE, and as the dementia progresses, the K-MMSE or the MMSE-2:BV may be more useful in clinical settings than the MMSE-2:SV or the MMSE-2:EV. Therefore, we found that the MMSE-2 can be more useful than the K-MMSE depending on the condition of various types of patients.

Third, as mentioned above, one of the purposes of developing the MMSE-2 is to use the same test across the world unlike the MMSE. Therefore, in this study, it is meaningful that the MMSE-2 is translated into Korean without modification and applied to the patients in Korean. According to the study of Folstein et al. (2010), when discriminating between the healthy older adults and the patients with dementia, the AUC was 0.84 in both the MMSE-2:SV and the MMSE-2:EV. In this study, when discriminating between the healthy older adults and the patients with AD, the AUC was 0.97 for the MMSE-2:BV, 0.95 for the MMSE-2:SV, and 0.94 for the MMSE-2:EV. Moreover, when discriminating between the healthy older adults and the patients with

VD, the AUC was 0.99 in the MMSE-2 (BV, SV, and EV). These results of this study showed that even though the MMSE-2 is not modified according to Korean culture, there is no difference in discriminating the healthy older adults and the patients with dementia using the MMSE-2 to Korean culture.

Limitations of this study and suggestions for future research are as follows.

First, the age and education level of the groups of the patients and the healthy older adults were not controlled. Although when statistical analysis was conducted, the differences of age and education level were controlled, but there was a disadvantage in that the range of age and education level was too wide when the participants in this study were included.

Second, in this study, we compared and analyzed the discriminant power of the MMSE-2 only in the groups (healthy older adults, MCI, VaMCI, AD, and VD). However, the MMSE-2 should be applied to a variety of different groups of dementia (PD, FTD, Huntington's disease, etc.). Therefore, it should be analyzed the differences in the

performance of the MMSE-2 in each group of patients to see how the MMSE-2 can be used clinically, and we also need to look at how the characteristics of the MMSE-2 change according to the group of patients.

Third, because this study is a cross-sectional study, this study focuses on evaluating the cognitive function of patients in the present. However, the continuous follow-up studies should be conducted to confirm the prognosis of patients. We should investigate whether the changes in the MMSE-2 score are sensitive to the progression of the disease of patients, and how the sensitivity of the MMSE-2 is different from other cognitive screening tests to determine whether the MMSE-2 can be used to evaluate the diagnosis and prognosis of the disease. Moreover, as with the MMSE, it should be examined whether the MMSE-2 can be continuously evaluated over time, and also in the future, it should be necessary to evaluate whether the MMSE-2 can be widely used in communities including public health centers as well as university hospitals.

Finally, in the previous studies, the Montreal Cognitive Assessment (MOCA) (Nasreddin et al., 2005), which includes a measure of the frontal lobe function among the various cognitive screening tests, was more sensitive than the MMSE in discriminating the patients with VCI from the healthy older adults (Xu et al., 2014; Dong et al., 2010; Bocti et al., 2013). In the MMSE-2, because the newly added tests such as the story memory and processing speed tests which can measure the frontal lobe function, it is necessary to compare the differences between the MOCA and the MMSE-2 to find out which test is more sensitive to detect cognitive decline of patients with VCI.

The prevalence of dementia has been gradually increasing as the elderly population increases in Korea. In the neuropsychological assessments which measure the cognitive function of patients with dementia, although there is a comprehensive battery that evaluates the various cognitive domains of patients in detail, it has been used in limited clinical scenes due to problems in temporal or cost. Therefore, the utility of screening tests, which can be used in various fields such as a public health center or a welfare institution for the elderly as

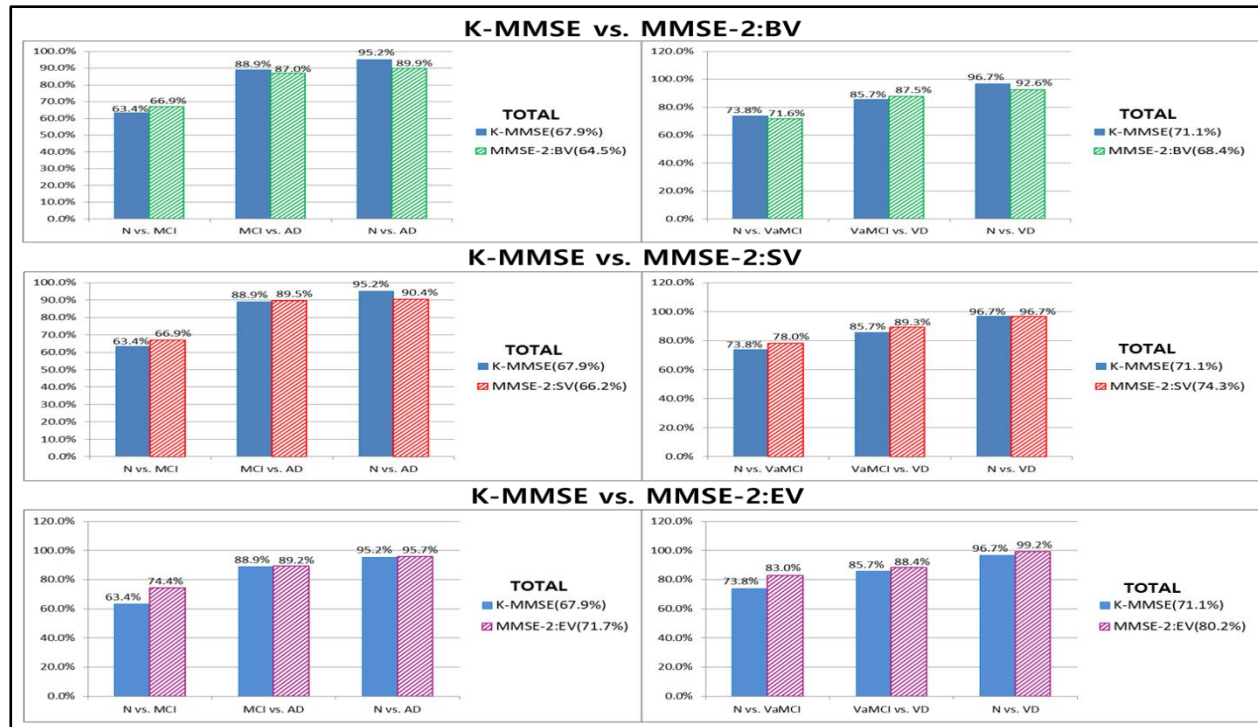
well as a hospital, has been increasing. Through this present study, we showed that the newly developed MMSE-2 (Folstein et al., 2010) as a cognitive screening test can be useful in clinical settings so we expect that the MMSE-2 will be widely used as a cognitive screening test in Korea.

Table 1. The AUC of the MMSE-2:BV, the MMSE-2:SV, and the MMSE-2:EV for the healthy older adults and the patients with MCI, VaMCI, AD, and VD

		N vs. MCI	MCI vs. AD	N vs. AD
MMSE-2	BV	0.71	0.93	0.97
	SV	0.72	0.93	0.95
	EV	0.73	0.92	0.94
		N vs. VaMCI	VaMCI vs. VD	N vs. VD
	BV	0.79	0.89	0.99
	SV	0.87	0.97	0.99
	EV	0.90	0.94	0.99

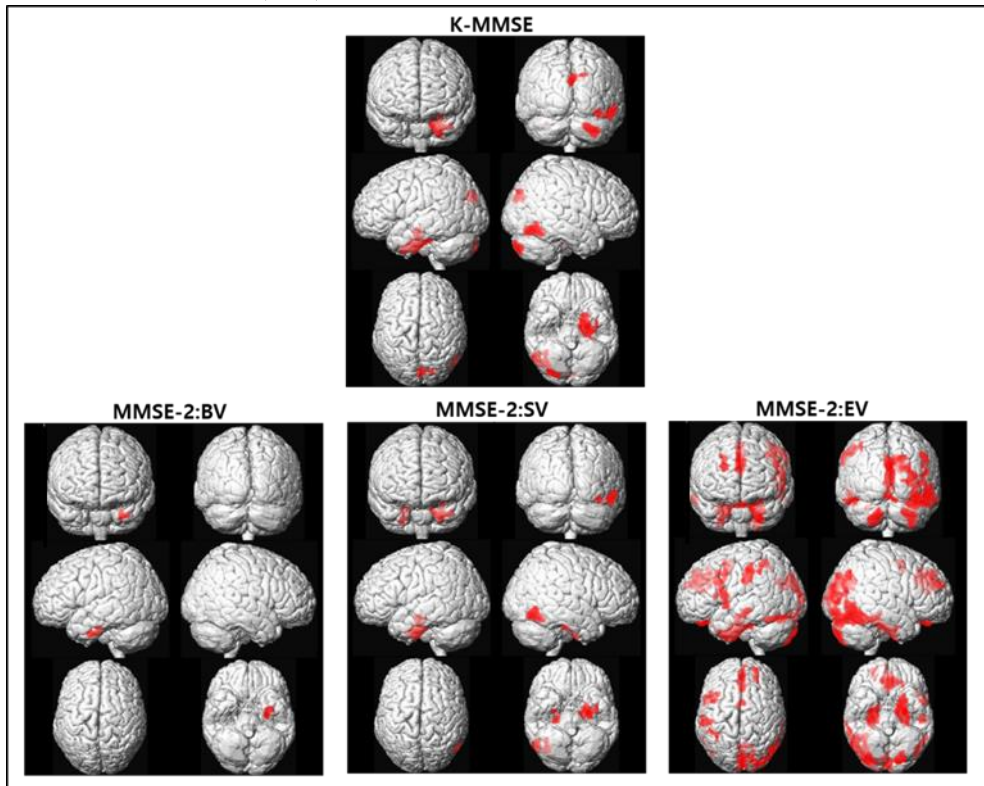
Abbreviations: AUC, Area Under the Curve; MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Figure 1. Comparison of classification rates (%) by discriminant analysis between the K-MMSE vs. the MMSE-2 (BV, SV, & EV)



Abbreviations: K-MMSE, Korean version of the Mini-Mental State Examination; MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version; N, Normal; MCI, Mild Cognitive Impairment; AD, Alzheimer's Disease; VaMCI, Vascular Mild Cognitive Impairment; VD, Vascular Dementia.

Figure 2. Comparison of the GM volume reduction correlated with the K-MMSE and the MMSE-2 (BV, SV, & EV)



Abbreviations: GM, Gray Matter; K-MMSE, Korean version of the Mini-Mental State Examination; MMSE-2, Mini-Mental State Examination-2; BV, Brief Version; SV, Standard Version; EV, Expanded Version.

Note.

Uncorrected $p < 0.005$.

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요약(국문초록)

인지기능을 측정하는 선별검사 중 세계적으로 가장 널리 사용되고 있는 검사는 Mini-Mental State Examination (MMSE) (Folstein 등, 1975)이다. 최근에 MMSE 의 단점을 보완하여 Mini-Mental State Examination, 2nd edition (MMSE-2) (Folstein 등, 2010)가 개발되었다. MMSE-2 는 기존 MMSE 의 형태를 유지하면서 언어적 기억력을 보다 자세하게 측정하는 이야기기억검사(story memory test)와 전두엽 기능 중 집행기능을 측정하는 스피드검사(processing speed test)가 포함되어 경도인지장애 환자나 초기 치매 환자들을 변별하는데 MMSE 보다 더 예민하다고 기대되고 있다. 따라서, 본 연구에서는 5 개의 연구를 통하여 한국어판 MMSE-2 를 제작하고, 신뢰도와 타당도를 측정하여, 한국판 MMSE-2 가 우리나라에서 임상적으로 유용하게 쓰일 수 있는지를 알아보고자 하였다.

연구 1 에서는 Folstein 등(2010)이 개발한 MMSE-2 를 한국어로 변환하였고, 이 검사가 정상노인집단, 경도인지장애 환자집단, 알츠하이머병치매 환자집단을 변별하는지에 대한 신뢰도와 타당도를 살펴본 결과, MMSE-2 의 타당도가 우수하고 신뢰도가 높아 한국에서도

인지기능 선별검사로서 유용하게 쓰일 수 있는 것으로 확인되었지만, 경도인지장애 환자들의 인지기능 저하를 탐지하는 능력은 기대만큼 예민하지 못한 것으로 확인되었다.

연구 2에서는 연구 1의 결과를 바탕으로 정상노인집단, 경도인지장애 환자집단, 알츠하이머병치매 환자집단을 대상으로 MMSE-2와 K-MMSE (Korean version of the Mini-Mental State Examination) (강연욱 등, 1997)중에서 어떤 검사 도구가 보다 정확하게 변별하는지 알아보려고 하였다. 그 결과, MMSE-2 검사 중 MMSE-2:SV (MMSE-2:Standard version)와 MMSE-2:EV (MMSE-2:Expanded version)가 K-MMSE 보다 초기 인지기능 저하를 더 민감하게 변별하였고, 치매가 진행이 될수록 K-MMSE 나 MMSE-2:BV (MMSE-2:Brief version)가 임상적으로 더 유용하게 쓰일 수 있는 것으로 나타나, MMSE-2가 임상현장에서 인지기능 선별검사로서 K-MMSE 보다 더 유용하게 쓰일 수 있는 것으로 확인되었다.

연구 3에서는 뇌 자기공명영상(Magnetic resonance imaging: MRI)을 이용하여 정상노인집단, 경도인지장애 환자집단, 알츠하이머병치매 환자집단의 K-MMSE와 MMSE-2의 결과와 두뇌 위축 정도의 상관관계를 살펴보았다. 그 결과, MMSE-2가 K-MMSE 보다 전반적인 뇌

영역의 위축 정도와 관련도가 높았다. 특히 MMSE-2:EV 가 전반적인 뇌 영역과 상관이 가장 높았고, K-MMSE 에서 측정하지 못하는 전두엽 기능도 측정할 수 있어서 MMSE-2 가 임상현장에서 인지기능 선별검사로서 K-MMSE 보다 더 유용하게 쓰일 수 있는 것으로 확인되었다.

연구 4 에서는 MMSE-2 소검사 중 집행기능을 측정하는 스피드검사와 언어적 기억력을 자세히 측정하는 이야기기억검사가 추가 되었기 때문에 MMSE 에서 변별하기 힘들었던 초기 혈관치매 환자들을 보다 더 민감하게 변별할 수 있을 것이라 예상되었다. 따라서, 정상노인집단, 혈관경도인지장애 환자집단, 혈관치매 환자집단을 신뢰롭게 변별하는지 신뢰도와 타당도를 살펴본 결과, 연구 1 에서처럼 MMSE-2 가 혈관 인지장애 환자들을 정상노인집단과 변별하는데 타당도와 신뢰도가 높게 나와 임상적으로 유용하게 쓰일 수 있는 것으로 확인되었다.

마지막으로, 연구 5 에서는 연구 4 의 결과를 바탕으로 정상노인집단, 혈관경도인지장애 환자집단, 혈관치매 환자집단을 대상으로 MMSE 와 MMSE-2 를 실시하여, 어떤 검사 도구가 보다 정확하게 변별하는지 알아보고자 하였다. 그 결과, 연구 2 에서처럼, 정상노인들과 혈관성 인지장애 환자들을 변별할 때도 MMSE-2:SV 와 MMSE-2:EV 가 K-

MMSE 보다 초기 인지기능 저하를 더 민감하게 변별하는 것으로 나타났고, 치매가 진행이 될수록 K-MMSE 나 MMSE-2:BV 가 더 유용하게 쓰일 수 있는 것으로 확인되었다. 따라서, MMSE-2 가 알츠하이머병 치매 환자들뿐만 아니라, 혈관성 인지장애 환자들을 대상으로도 임상 장면에서 인지기능 선별검사로서 K-MMSE 보다 더 유용하게 쓰일 수 있는 것으로 확인되었다.

본 연구를 통하여 새롭게 개발된 MMSE-2 (Flostein 등, 2010)가 현재 널리 사용되고 있는 MMSE 보다 경도인지장애 환자나 초기 치매 환자들을 변별하는데 더 민감하고, 임상적으로 유용하게 쓰일 수 있음을 보여주었다. 따라서, 앞으로 일차병원, 보건소, 노인복지관 등에서 일차 인지기능 선별검사로서 널리 사용된다면, 조기 치매 발견에 도움을 줄 수 있을 것이라 기대된다.

주요어: MMSE, MMSE-2, K-MMSE, 경도인지장애, 알츠하이머병치매, 혈관경도인지장애, 혈관치매

학 번: 2015-30006